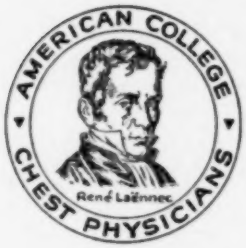
VOLUME XVIII NUMBER 4

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



PUBLISHED MONTHLY

OCTOBER
1950

EXECUTIVE OFFICE, 500 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS
PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS

Entered as Second Class Matter August 18, 1936, at the Postoffice at El Paso, Texas
Under the Act of Congress of August 12, 1912.

A New Pleasant Tasting–

BACITRACIN TROCHE

WITH BENZOCAINE

FOR CONTROL OF LOCAL DISCOMFORT

The clinical efficacy of bacitracin troches has been further expanded by the incorporation of 5 mg. of benzocaine per troche. The local anesthetic action so provided, in addition to the specific antibiotic effect of the bacitracin, makes for a wider field of usefulness in the treatment of pharyngitis, tonsillitis, and gingivitis. These troches remain intact for a prolonged period thereby exerting an extended anesthetic influence and creating high salivary bacitracin levels.

The confection-like chocolate taste of C.S.C. Bacitracin Troches with Benzocaine makes for universal patient acceptance. Their candy-like taste and appearance encourage their continued use by adults as well as by older children.

C. S. C. Bacitracin Troches with Benzocaine are available on prescription through all pharmacies in bottles of 25.

C.S.C. Pharmaceuticals A DIVISION OF
COMMERCIAL SOLVENTS CORPORATION
17 EAST 42ND STREET, NEW YORK 17, N.Y.

CSC

Each C.S.C. Bacitracin Troche with Benzocaine contains
1000 UNITS OF BACITRACIN AND 5 MG. OF BENZOCAINE

DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
500 North Dearborn Street, Chicago 10, Illinois
MURRAY KORNFELD, *Managing Editor*

VOL. XVIII OCTOBER 1950 No. 4

CONTENTS:

Entered as second class matter, August 18, 1936, at the postoffice at El Paso, Tex., under the Act of Aug. 24, 1912.

Annual Subscription: United States of America $8.50
Foreign Countries $9.50

a **new**

antibacterial

agent . . .

Wide antibacterial activity, low toxicity and virtual elimination of renal complications distinguish the use of Gantrisin* 'Roche', a new and remarkably soluble sulfonamide. Highly effective in urinary as well as systemic infections, Gantrisin does not require alkali therapy because it is soluble even in mildly acid urine. More than 20 articles in the recent literature attest its high therapeutic value and the low incidence of side-effects. Gantrisin is now available in 0.5 Gm tablets, as a syrup, and in ampuls. Additional information on request.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Gantrisin®

** Brand of sulfisoxazole (3, 4-dimethyl-5-sulfanilamido-isoxazole)*

'Roche'

Chronic Asthmatic

. . . back in the social swing

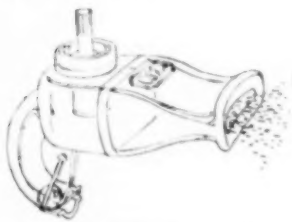
WHEN she feels an attack coming on, she simply reaches into her purse, takes out the Aerohalor* and takes three or four inhalations of a bronchodilating powder called NORISODRINE Sulfate. The bronchospasm ends quickly.

This take-it-with-you therapy is effective against both mild and severe asthma, has restored many chronic asthmatics to normal activity. Proved by clinical investigation,[1,2] NORISODRINE has relatively low toxicity. Few side-effects result when the drug is properly used and, when they do, are usually minor.

Before prescribing NORISODRINE, however, please write for literature which discusses dosage and precautions. NORISODRINE Sulfate powder 10% and 25% is supplied in multiple-dose Aerohalor* Cartridges, packaged three to an air-tight vial. Aerohalor is prescribed separately.

Abbott Laboratories, North Chicago, Illinois. Abbott

*Trade Mark for Abbott Sulfate Cartridge
†Abbott's Powder Inhaler



NOTE THE NAME

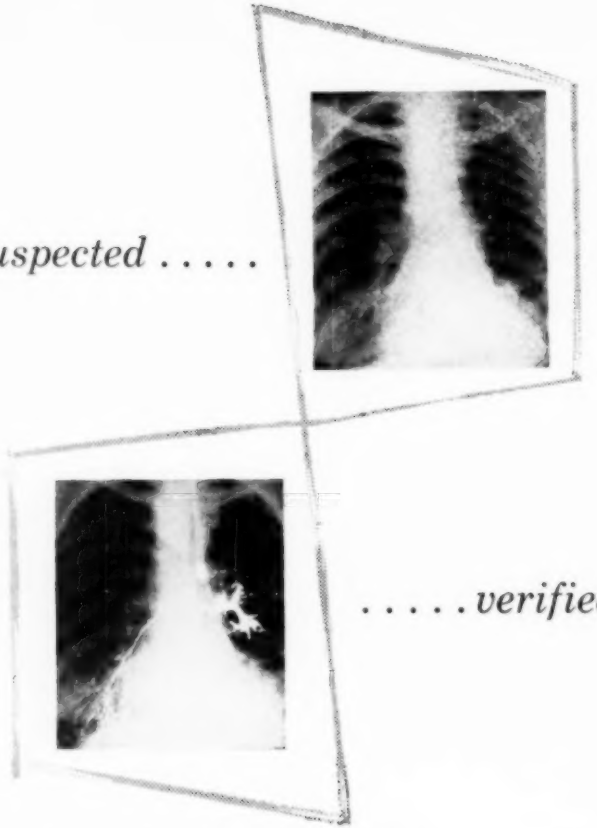
NORISODRINE Sulfate Powder

(ISOPROPYLARTERENOL SULFATE, ABBOTT)

Always Ready for Use when the Need Arises

1. Krasno, L. R., Grossman, M. I., and Ivy, A. C. (1949). The Inhalation of 1-3', 4'- Dihydroxyphenyl-2-Isopropyl-aminoethanol (Norisodrine Sulfate Dust). J. Allergy, 20:111, March. 2. Krasno, L. R., Grossman, M., and Ivy, A. C. (1948). The Inhalation of Norisodrine Sulfate Dust, Science, 108:476, Oct. 29.

suspected . . . . .



. . . . . verified

. . . Lipiodol*

completes the diagnostic picture

From its introduction to the present, Lipiodol has remained a contrast medium of choice . . . notable for these properties: **1** 40% iodine content firmly bound in poppyseed oil, insures uniform radiopacity **2** viscosity characteristics produce clear delineation without excessive "pooling" **3** exclusive formulation does not involve use of chlorine or its derivatives **4** its blandness insures minimal irritation to mucous membranes.

*Lipiodol (Iodized oil, U. S. P.) is the registered trade mark for the original product created by Lafay. This product alone can bear the name Lipiodol. Made in the U. S. A. E. Fougera & Co., Inc. New York. N. Y. Canadian Distributors: Vinent, Ltd., Montreal, Canada.

Davidson's
PNEUMOTHORAX APPARATUS

Designed by

Dr. Louis R. Davidson

New York City

Complete with tubing and two needles

$115.00

THIS apparatus was designed to perform all the functions that any pneumothorax instrument may be called upon to render.

Simple, practical, foolproof and portable, it supplies the medical profession with an apparatus that can be used to maximum advantage, and under all circumstances in the office, the hospital or the patient's home.

Its many advantages—initial filling under theoretically exact conditions—refills correctly measured—production of high intrapleural pressure when required—removal of air from pleural cavities as in spontaneous pneumothorax—have been realized by an ever increasing number of physicians now using the lung collapsing technique in the treatment of tuberculosis.

Sturdy and dependable, all the features of this instrument are highly perfected.

"The Evolution of Modern Pneumothorax Machines," by Dr. Louis R. Davidson, reprinted from the American Review of Tuberculosis, November 1939, together with descriptive literature will be mailed on request.

Sold Only Through Surgical Supply Dealers

Developed and Produced by

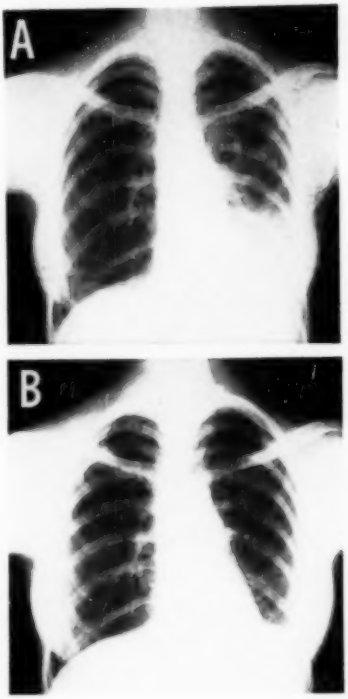
Sklar LONG ISLAND CITY, N. Y.

Effective Chemotherapy in TUBERCULOSIS

DIHYDROSTREPTOMYCIN or Streptomycin, used alone or in combination with para-aminosalicylic acid, is recognized as a valuable and, in some instances, an essential adjuvant in the treatment of selected types and stages of tuberculosis.

Para-aminosalicylic acid is capable of inhibiting or significantly delaying the emergence of bacterial resistance to dihydrostreptomycin or streptomycin.

These drugs are not to be regarded as substitutes for traditional therapeutic methods. Rather, they serve best when properly integrated with bed rest and, where necessary, collapse measures or other forms of surgery.



A. Before Treatment
(9 days prior to Dihydrostreptomycin therapy) Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).

B. After 3 Months' Treatment
(2 days after discontinuance of Dihydrostreptomycin) Considerable clearing of acute exudative process in the diseased lung; cavity smaller and wall thinner.

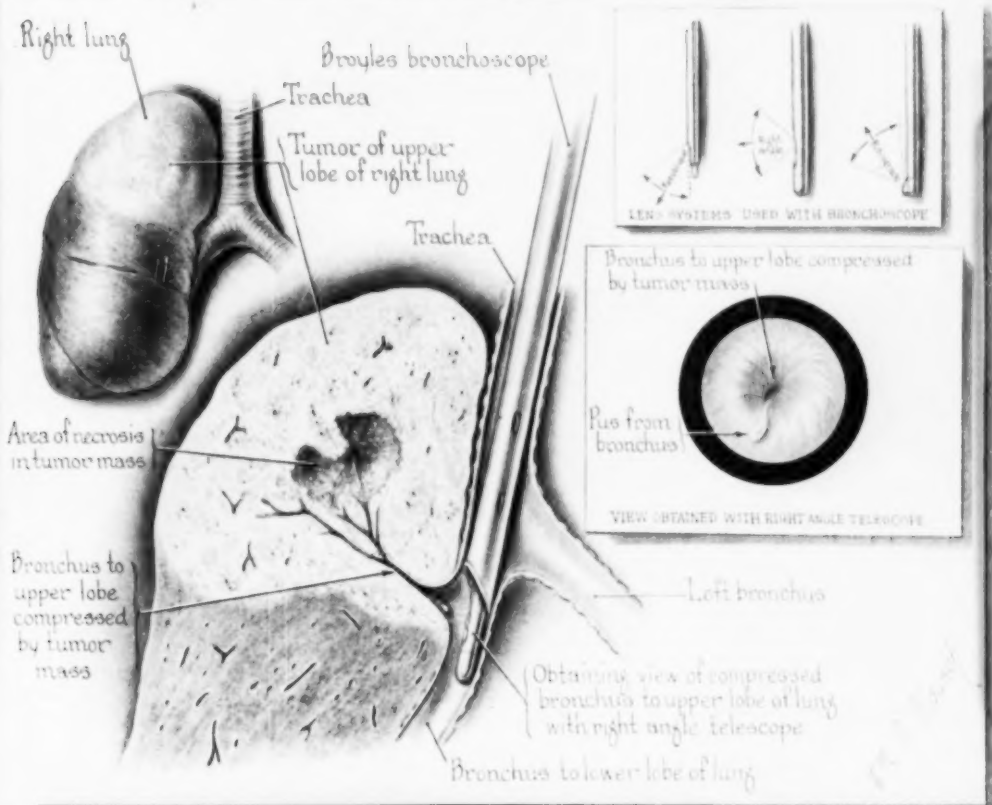
Detailed literature on the subject of chemotherapy in tuberculosis will be supplied upon request.

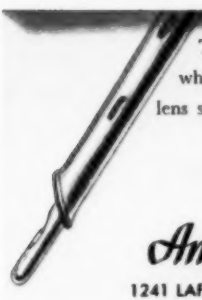
MERCK & CO., Inc.
Manufacturing Chemists
RAHWAY, NEW JERSEY

Merck Antituberculosis Agents

Streptomycin Calcium Chloride Complex Merck	Para-Aminosalicylic Acid Merck (PAS)	Crystalline Dihydrostreptomycin Sulfate Merck

THE *Broyles* BRONCHOSCOPE





The illustration shows a case of suspected tumor of upper lobe of right lung in which x-ray findings were inconclusive. The Broyles Bronchoscope with right angle lens system disclosed a compressed bronchus, and a diagnosis of tumor was made.

ESTABLISHED IN 1900 BY REINHOLD WAPPLER

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE NEW YORK 59, N. Y.

Heyden PENICILLIN *and* STREPTOMYCIN

FROM CULTURE TO CONSUMER . . .

UNDIVIDED RESPONSIBILITY!

The exceptional quality of Heyden antibiotics—the high-assay and outstanding purity of Penicillin and Streptomycin products—is the direct result of pioneering experience, intensive research, and advanced manufacturing methods. Accuracy of control and constant supervision—undivided responsibility from original culture to final production and delivery—are your guarantee of unvarying uniformity and assured results.

All of the Penicillin and Streptomycin products listed here are produced in Heyden's own extensive laboratories and plant at Princeton, N.J. They are shipped direct to medical and hospital consumers, and to ethical manufacturers and packagers who market these Heyden antibiotics under their own labels.

PENICILLIN PRODUCTS

Crystalline Penicillin G Sodium or Potassium (in vials); Crystalline Procaine Penicillin G in Sesame Oil with 2% Aluminum Monostearate w/v (cartridges, single- and multiple-dose vials); Crystalline Procaine Penicillin G for aqueous injection (single- and multiple-dose vials of "PPA".)

Tablets: Buffered Crystalline Penicillin G Potassium (50,000, 100,000 and 250,000 units, sealed in foil, for oral use.)
Crystalline Penicillin G Potassium Soluble (50,000 and 100,000 units, sealed in foil, for oral use.)

Troches: Crystalline Penicillin G Potassium, (5,000 and 10,000 units, sealed in foil. Pleasingly flavored, slow to dissolve.)

STREPTOMYCIN PRODUCTS

Crystalline Dihydrostreptomycin Sulfate (1-gm. and 5-gm. multiple-dose vials.)
Streptomycin Sulfate (1-gm. and 5-gm. multiple-dose vials.)
Dihydrostreptomycin Sulfate.

OF INTEREST TO MANUFACTURER-DISTRIBUTORS

Heyden's unusual and exclusive service to packagers of Penicillin and Streptomycin products protects YOUR sales and profits under YOUR OWN NAME. Specially designed prescription-type cartons and unit containers are ready for your specific labelling. Technical literature, brochures and instruction inserts are supplied without cost. Write today for detailed particulars.

CONSIDER THE SOURCE! . . . AND YOU'LL SPECIFY HEYDEN

FINE HEYDEN CHEMICALS

HEYDEN CHEMICAL CORPORATION

Professional Products Division

225 WEST 34th STREET • NEW YORK 1, N.Y.

DISEASES *of the* CHEST

VOL. XVIII OCTOBER 1950 NUMBER 4

Extrapleural Pneumonolysis with Lucite Ball Plombage*

O. C. BRANTIGAN, M.D., F.C.C.P. and
H. L. RIGDON, M.D.
Baltimore, Maryland

If the prophylaxis of pulmonary tuberculosis were as effective as prophylaxis in smallpox, diphtheria, or typhoid fever there would be little need to do more than continue the search for a more effective antibiotic agent to combat the disease. Even without streptomycin as an aid the medical treatment of pulmonary tuberculosis will arrest the disease in the vast majority of patients who become sick from pulmonary tuberculosis. When medical treatment fails to arrest pulmonary tuberculosis it is usually because the disease is too far advanced before the patient is presented for treatment. However, when medical means fail to arrest the disease, surgical measures are added as an adjunct to medical treatment. Three types of surgical treatment are available: excisional surgery, cavitary drainage, and collapse therapy. There have slowly been developed some definite indications and contraindications for a particular type of surgery. There is, however, a group of patients whose disease is of such character that it does not clearly fit into definite indications or contraindications for a particular type of surgical treatment. Accordingly, there will always be a difference of opinion concerning the choice of operation and for this reason there will always be a fairly high percentage of surgical failures.

Excisional surgery for pulmonary tuberculosis is predominately reserved for unilateral disease and it has a variable mortality rate and cure rate. Overholt[1] reported 88 patients who had 92 pulmonary resections in the treatment of tuberculosis and these were followed from two to 12 years. Of 33 patients with lobectomies 43 per cent are well and have negative sputum; 18 per cent are dead.

*From the Department of Surgery, Baltimore City Hospitals, and the Department of Surgery, School of Medicine, University of Maryland.

Among 58 patients with pneumonectomies 48 per cent are well and have negative sputum; 41 per cent are dead. Bailey[2] reported 100 patients with pulmonary resections done in the prestreptomycin era who were followed from one to eight years, and 100 patients who received streptomycin and were followed less than three years. In the prestreptomycin group 55 per cent are well and have a negative sputum, and 37 per cent are dead; in the group treated with streptomycin 77 per cent are well and have negative sputa, and 16 per cent are dead. Among 51 patients who had pulmonary resections for tuberculosis the authors[3] found in the prestreptomycin group 50 per cent who are well and have negative sputa, and 30 per cent who are dead; in the group of 29 patients treated with streptomycin 28 are living; 76 per cent of these are well and have negative sputa. There is constant study of the excisional type of surgery in order to develop more rigid and better understood indications and contraindications for operation.

In cavitary drainage it is impossible to give any significant statistics since open drainage is usually secondary to some previous operative procedure and closed or Monaldi drainage is generally used as a palliative procedure or a preliminary to thoracoplasty.

Collapse therapy can be divided into two main groups, reversible or temporary collapse as represented by pneumothorax and temporary phrenic paralysis, and irreversible or permanent collapse treatment as represented by standard thoracoplasty and its modifications and the various plombage operations. The failure of a good pneumothorax to arrest all patients thus treated merely proves that collapse therapy is not an effective method of treatment in all patients with pulmonary tuberculosis. In 608 persons who had pneumothorax and closed pneumonolysis and were followed for one to eight years by one of the authors,[4] 69 per cent of the white were well and had negative sputa; only 24 per cent of the negroes were well, with negative sputa. There were 133 negroes. Allen and Kelly[5] reported 56.3 per cent satisfactory results in 128 patients who were followed for two years after electively ending pneumothorax treatment; twelve of these patients had bilateral pneumothorax. If the selection of patients for pneumothorax were better understood the disease would be arrested in a higher percentage of patients treated.

The standard thoracoplasty has slowly evolved to its present state. One of the authors studied the results of thoracoplasty on 337 patients whose operations were completed before 1942. They were followed from two to nine years and it was found that 40.6 per cent were dead, with 2.7 per cent dying from causes not related to tuberculosis or its treatment. In the remaining 200 patients 89.5 per cent were well and had negative sputa. These, however,

constituted 48 per cent of the original number. It is interesting to note that of the whole group 50 per cent of the white and only 36 per cent of the negro patients were well and had negative sputa. Davison[6] reported a follow-up of from one to 12 years on 888 patients who had thoracoplasties and found 19 per cent dead. In considering the original group 55 per cent are apparently arrested. Kinsella[7] reported a follow-up of from five to 26 years on 613 patients who had thoracoplasties and found 33.1 per cent dead, with 5.5 per cent dying from causes not related to tuberculosis or its treatment. Those living showed 88 per cent well, with negative sputa. It is difficult to calculate the percentage of the original number with negative sputa but it cannot be higher than 66.9 per cent, since 33.1 per cent are dead. Douglas[8] described 102 patients who had thoracoplasties and were followed for five years; he found only 14 per cent dead and 69 per cent well and with negative sputa. As the indications for thoracoplasty are better understood and the operative technique becomes more perfected one can reasonably expect a lower mortality rate and a higher cure rate.

The extrapleural pneumothorax (pulmonary plombage with air) has been severely criticized as an ineffective operative procedure frought with many and serious complications. Nevertheless in Friedman's[9] discussion of the operation he says, "Perhaps the almost uniformly poor results reported by these investigators following their use of extrapleural pneumothorax reflects their inexperience with this particular type of procedure and poor choice of patients rather than a condemnation of the particular form of therapy." After giving various statistical figures concerning end results he writes, "In fact, the results by comparison are as good or better than those obtained with other more generally practiced forms of collapse therapy."

Wilson[10-13] developed the lucite spheres as a method of pulmonary plombage in the collapse treatment of pulmonary tuberculosis. Lucite had the advantage of being: (1) nonirritating to tissue; (2) noncarcinogenic and nonantigenic; (3) insoluble; (4) only slightly resistant to roentgen rays; (5) round and easily fitted into any space; (6) light in weight so there would be no erosion or migration caused by weight. Furthermore, if fluid developed the balls would float. His results as reported were gratifying. Grow[14,15] was favorably impressed by the operation in the beginning but he was not enthusiastic about the procedure in 1949. Dolley[16] is in favor of the operation as used in thoracoplasty failures. Trent,[17] Murphy,[18] O'Brien[19] and Walkup[20] are definitely opposed to the operation.

Much of the opposition to extrapleural pneumonolysis with lucite ball plombage originates from the report by Trent.[17] A summary

of his report on 51 patients is indeed discouraging and reveals in nearly all patients the disease was classified as far advanced. All but three patients had bilateral disease. "Thirteen patients were considered unsuitable for any type of surgical collapse " The early complications amounted to 39.3 per cent of the patients. There were eight operative deaths; three, cavity entered at operation; three, spread of disease; two, dissection of spheres; two, compression of superior vena cava; one, wound separation. The late complications amounted to 31.3 per cent of the patients. They were 11, tuberculous infection about the spheres; four, draining sinus; four, spheres extruded beneath skin; one, migration of spheres into mediastinum. The end results were, improved 19.6 per cent; unimproved, 5.8 per cent; worse, 39.2 per cent; dead, 35.3 per cent.

It seems that criticism directed at the operation is probably unjust. By using lucite ball plombage a collapse equal to or better than thoracoplasty can be obtained by a simple, nondeforming, one stage operation. Therefore, the method of treatment should not be discarded as unsatisfactory without careful consideration of the indications, contraindications, and the surgical technique.

The authors have used the method on 64 patients since June 1947 and a careful study of the patients and the results apparently justifies a report concerning the patients and a continued favorable interest in the operation.

Seventy-two lucite ball plombage operations were performed on 64 patients between June 1947 and December 1948. Eight of the patients had a bilateral plombage operation. Six patients were negroes and 58 were white; there were 40 females. In the group 42 patients were between the ages of 28 and 48 years. In 13 the contralateral lung was under collapse therapy at the time of the plombage operation, four had thoracoplasty, and nine had pneumothorax. The patients were in good general physical condition but some were poor surgical risks when the extent of the disease was considered.

All the operations except two were done under paravertebral block with procaine, 1 per cent, and local infiltration of procaine, 0.5 per cent. The patients were given 3 grains of pentobarbital sodium one hour before operation. On call to the operating room morphine sulfate in doses of 0.125 to 0.25 grains was given, depending upon the size and reaction of the patient. Anesthesia was uniformly good, but since it requires about two hours to inject the anesthetic and complete the operation many patients became tired and had cramps in the arm and shoulder upon which they were lying.

The patient is placed in a true lateral position and a curved

posterior incision is made in the interscapular region. A section of the fourth rib and transverse process is removed in a subperiosteal manner. The extrapleural plane is developed. In the first few patients the lung was freed from the mediastinum as well as from the chest wall, but since this appeared to permit downward displacement of pulmonary cavities the freeing of the lung from the mediastinum was abandoned. Care is taken to free the lung wall forward approximately to the internal mammary artery and posteriorly beyond the sympathetic trunk. The extrapleural stripping is carried to the inferior limit of the disease as indicated by palpation and roentgenogram. The lucite spheres are placed in the extrapleural space without tension. The extent to which the extrapleural space is developed is of the utmost importance and not the number of lucite spheres used. The rib bed is carefully closed with interrupted silk sutures. Silk is used throughout the operation. Under rigid aseptic technique the lucite spheres are sterilized by immersion in aqueous zephiran, 1:1000 for 18 to 24 hours. The lucite balls are rinsed thoroughly in normal saline solution and then placed in a solution of azochloramid, 1:3300, in sodium tetradecyl sulfate, 1:500, in a sterile container on the instrument table. They are removed from the latter solution and placed in the extrapleural space without drying.

The patients are given 2.0 gm. of streptomycin daily in divided doses for from two to five days before operation. They are also given 7.7 gm. each of sulfamerazine and sulfadiazine every four hours for about 48 hours preoperatively. After operation the sulfonamides are discontinued and penicillin is administered in 50,000 unit doses every three hours. The penicillin is continued until the skin sutures are removed on the fifth to seventh day. Streptomycin is continued postoperatively in divided doses of 2.0 gm. daily until the temperature is normal, usually three or four days, and the quantity of the streptomycin is then reduced to 0.5 gm. every 12 hours until the patient is discharged from the hospital on about the tenth to fourteenth day. Whether streptomycin is to be continued after discharge from the surgical ward depends upon the decision of the medical doctor who cares for the patient after his discharge from the surgical service.

The follow-up has been complete but of limited duration, extending from six months to two years. The patients were referred from many sources, including various sanatoriums and private physicians. The presence or absence of tubercle bacilli is at least on repeated direct smear or sputum, but many have had negative cultures of the sputa and gastric contents. Of the group 27 (42.2 per cent) have positive sputa, and 35 (54.7 per cent) have negative sputa. Two (3.1 per cent) are dead. Of the 27 who have positive

sputa 20 have the disease in the contralateral lung and in no instance is it a spread of the disease after operation. Of the eight patients who had bilateral plombage four have negative sputa. In order to make a proper evaluation one must separate the patients with definite contralateral disease from those with an undiseased lung on the opposite side. It also gives a better understanding if one separates the patients with bilateral plombage from those with an undiseased opposite lung. Thus on removing 28 patients from the original 64 there remain 36 with no roentgenographic evidence of disease in the opposite lung at the time of follow-up evaluation. The results then are two dead (5.5 per cent), three (8.3 per cent) with positive sputa, and 31 patients (86.1 per cent) well and with negative sputa. There are six negro patients and three are well with negative sputa and three have positive sputa; one of these has disease in the opposite lung. One of the two deaths occurred three days after operation from profound spread of the disease on both sides. This patient had a spreading lesion that was thought to be controlled by streptomycin. He underwent a rather extensive plombage operation although he should have been refused surgical treatment. The other death occurred from tuberculous meningitis several months after the plombage operation. It was a flare-up of tuberculous meningitis that was treated by streptomycin before the plombage operation. This condition was thought to be cured.

Following operation there were two patients with pneumothorax on the operated side and in each instance it absorbed spontaneously. In one patient there was bleeding into the extrapleural space after operation. He was aspirated on two occasions and received two 500 cc. blood transfusions. When the excess blood was absorbed the lucite spheres were localized in the apex of the thorax where they were formerly placed. No other postoperative complication has appeared, either early or late, nor has there been any infection of the wound or extrapleural space. There has been no migration of the lucite balls and no other spread of the tuberculous disease. At a period not earlier than eight weeks after operation a flare-up of previously existing tuberculous disease in the opposite lung was noticed and in three patients there was a flare-up of disease in the lung below the area collapsed by the lucite spheres.

It is common to find several different tuberculous pathologic reactions not only in the two lungs of one patient, but within the same lobe of one lung. It is not uncommon to find cavitation, areas of fibrosis, and even caseation all within the same lobe of the lung. Under such conditions of disease why should not the reaction to surgical treatment be highly variable? The variability of the path-

ologic process makes it extremely difficult to choose the right operative procedure. Often the choice of surgery is made because of the predominant pathologic process, which in turn may respond well to treatment only to have a supposedly minor area of disease react badly and thus cause failure of treatment to convert the positive sputum.

It is obvious that collapse of the lung will not cure all types of tuberculosis pathologic processes in the lung; if this were true no other method of treatment would be necessary. However, where collapse of the lung is thought to be the surgical treatment of choice it is evident that collapse by extrapleural plombage can equal or surpass the collapse produced by any other surgical measure, except a good pneumothorax without adhesions. If the complications can be kept at a minimum or can be eliminated entirely there can be no true criticism of the procedure since it is simpler than all other methods of collapse treatment, except perhaps temporary phrenic paralysis. Treatment by pneumothorax may be complicated by generalized empyema and the possibility of an unexpandable lung at the termination of treatment.

In the event extrapleural plombage with lucite balls is unsafe because of complications or if the end results are not as satisfactory as desired, then a study of the procedure should be made to discover the reasons for complications and for failure to cure the patient. The procedure should not be condemned without a fair trial. The authors have eliminated the complications incidental to the operative technique and to the pleura and the extrapleural space. Early and late flare-up of pre-existing lesions have been kept at a minimum, but with the adoption of certain criteria it probably can be reduced further. Attention has been given to final end results and it is thought that a definite reason for failure has been demonstrated.

Complications incidental to the operative technique, pleura, and extrapleural space have been eliminated with the use of local anesthesia, the posterior operative approach, silk suture technique, and an adequate use of the available chemotherapeutic agents. The posterior surgical approach gives access to the area of disease since the majority of tuberculous pulmonary pathologic processes are in the posterior aspect of the lung. The diseased lung and the pleura are less likely to be entered when they are directly exposed. The desired extent of collapse can be accomplished more readily by the posterior approach. Local anesthesia forces the surgeon to be gentle with the tissues and lessens the chance of spread and flare-up of existing disease. The use of penicillin, streptomycin, and sodium tetradecyl sulfate in azochloramid, together with silk suture technique should eliminate extrapleural space infection.

Pneumothorax caused by a tear in the pleura or spontaneous from the lung has presented no serious problem during or after operation. Failure to accomplish the operation occurred in only one patient.

The plombage with lucite spheres seems safer than the collapse that is maintained with air. The lucite spheres stimulate a thin, strong, dense, fibrous tissue membrane that encases the spheres in individual tissue cells or communicating adjacent cells. The strong, dense, fibrous tissue membrane is likely to prevent erosion of disease beyond its surface. Air does not stimulate a fibrous tissue reaction of this type. In the past other material used for pulmonary plombage has not stimulated a corresponding thin layer of strong, dense, fibrous tissue. With lucite spheres there is no need for repeated needle punctures, for refills of air, or for the aspiration of fluid, thus reducing the chances for contamination of the extrapleural space by the needle, either from without the body or from puncture of the normal or diseased lung. Since lucite material is light it is less likely to migrate or erode the tissue than any other type of plombage material used in the past. Because the lucite balls are encased in a thin, dense, fibrous tissue membrane there can be no migration. However, if infection prevents the formation of this fibrous tissue membrane there can be migration. There can be no migration without infection. Should infection of the extrapleural space occur it seems reasonable that the lucite spheres should be removed promptly before migration or erosion occurs. In the one patient who had postoperative bleeding extensive enough to strip the pleura to the region of the diaphragm, the lucite spheres were located in the apex when the blood had completely disappeared by aspiration and absorption.

A flare-up of disease in areas inferior to the lucite balls has occurred in three patients; in two of these an attempt was made to increase the collapse by the introduction of more lucite spheres, but at operation it was mechanically impossible to accomplish effective additional collapse and neither patient was improved. The inability to increase the extent of collapse should it become desirable after the original operation has led to the conclusion that evidence of disease below the seventh rib posteriorly is a contraindication to plombage. Such patients should be subjected to thoracoplasty since the extent of collapse can be increased should it become necessary. There has been no evidence of a flare-up of disease in the opposite lung resulting from extrapleural plombage. However, there has been no instance in which the lesion in the opposite lung was immediately improved by the plombage operation. The same is true of pulmonary resection for pulmonary tuberculosis. It is not unusual, however, to find that

thoracoplasty on one side will help a lesion in the opposite lung, probably by causing the mediastinum to shift sufficiently to the unoperated side to relax the lung. It is possible that a more extensive collapse should be carried on in the plombage patient with disease in both lungs. However, the patient with bilateral apical disease probably should have bilateral collapse planned in the beginning; therefore plombage would be superior to thoracoplasty since it is more conservative of lung tissue and the cardiorespiratory function than is thoracoplasty.

It is evident that the end results will either establish or eliminate extrapleural lucite ball plombage as an acceptable operative procedure in the treatment of pulmonary tuberculosis. The series reported surely removes all other criticism directed at the operative procedure.

There is no standard by which end results can be evaluated justly. If all patients subjected to the operation are considered the results are poor; only 54.7 per cent have negative sputa. Nevertheless they are not too different from the results of thoracoplasty (Chart I). If only the patients with unilateral roentgenographic evidence of disease at the time of the follow-up study are considered the results are highly gratifying; 86.1 per cent have negative sputa. In bilateral pulmonary tuberculosis it seems that the greatest failing has been to surgically collapse only one side, attacking, of course, the side with the greater amount of disease. Perhaps if more patients had bilateral collapse there would be a larger percentage with negative sputa. This assumption is not borne out in eight patients with bilateral plombage since negative sputa has been obtained in only one-half of them. Where there is bilateral surgical treatment the question arises as to whether one should expect half as many cured patients or twice as many sick ones. In quoting end results one should distinguish between primary plombage and plombage after thoracoplasty. This paper deals only with primary plombage. Intrapleural lucite ball prosthesis after pneumonectomy should be considered separately. A study of patients who continue with positive sputa after plombage forces certain conclusions.

The lung should not be freed from the mediastinal pleura. If it is so freed the diseased lung can be pushed or can descend into healthy lung tissue without collapsing. Most workers abandoned the Simbs' apicolysis after thoracoplasty for this reason. In reviewing the results of thoracoplasty the authors found a lower percentage of conversion of sputum after Simbs' apicolysis than without it. Perhaps better bronchial drainage is favored if the lung is held suspended superiorly along the mediastinum. The high adherence of the lung along the lateral chest wall should

RESULTS OF SURGICAL TREATMENT OF TUBERCULOSIS

Author	Type of Treatment	Number of Patients	Well—Sputum Negative (Per cent)	Dead (Per cent)	Follow-Up
Overholt	Lobectomy	33	43	18	2 yrs. to 12 yrs.
Overholt	Pneumonectomy	58	48	41	2 yrs. to 12 yrs.
Bailey	Resection—				
	Prestreptomycin	100	55	37	1 yr. to 8 yrs.
	Poststreptomycin	100	77	16	Less than 3 yrs.
Brantigan and Rigdon	Resection—				
	Prestreptomycin	21	50	30	1 yr. to 6 yrs.
	Poststreptomycin	29	76	3.4	6 mos. to 3 yrs.
Brantigan	Pneumothorax and Pneumonolysis	608	69		1 yr. to 8 yrs.
Allen and Kelly	Pneumothorax	128	56.3		2 yrs.
Brantigan	Thoracoplasty	337	48	40.6	2 yrs. to 9 yrs.
Douglas	Thoracoplasty	102	69	14	5 yrs.
Davison	Thoracoplasty	883	55	19	1 yr. to 12 yrs.
Trent	Plombage	51	19.6	35.3	6 mos. to 34 mos.
Brantigan and Rigdon	Plombage				
	(All Patients)	64	54.7	3.1	6 mos. to 24 mos.
	(Unilateral Disease)	36	86.1	5.5	6 mos. to 24 mos.

be avoided. It produces a U-shaped collapse which is unfavorable.

It has been found impossible to collapse the lung in areas below the apex without freeing the apex of the lung and permitting it to collapse. Therefore, extrapleural lucite ball plombage is indicated only in apical disease.

The earlier tendency was to do a limited plombage, thus conserving all possible lung tissue. In the experience of the authors most patients subject to thoracoplasty required a six or seven rib operation. The plombage operation, for about the same amount of disease, has not nearly equalled the same amount of collapse. This, perhaps, is a mistake. However, if the extent of collapse is increased one can expect an increase in postoperative complications, particularly a flare-up of disease on either side at the time of operation. The one postoperative death reported was from this cause. The collapse probably should not be carried farther than the third interspace anteriorly and the upper aspect of the seventh rib posteriorly. Thus, extrapleural plombage should be reserved for apical disease. If more extensive collapse is needed thoracoplasty should be used since it can be done in multiple stages, whereas plombage is a single stage operation.

There are certain contraindications to the plombage operation and for the most part these are the contraindications to collapse therapy generally, namely, giant cavities, large tension cavities, tuberculomas, spreading acute disease, and the so-called destroyed lung. Added to these and specifically indicated for plombage is extensive disease from apex to base. Plombage for giant cavities and large subpleural tension cavities is likely to result in erosion of the cavity into the extrapleural space.

It is often difficult to resist the plea of the patient and the referring doctor when contraindications are borderline or slightly but definitely beyond the scope of the plombage operation. Frequently the patient and the referring doctor are unwilling to agree at the outset to bilateral collapse. In treating patients with bilateral disease this results in many failures because when the patient is freed of all symptoms and is clinically well except for positive sputum he will often refuse to undergo the second operation. Since these patients have positive sputum they are classified as failures of treatment. This leads to the question of whether they are failures and whether one can be satisfied with improving the condition of the patient but not converting the sputum.

Perhaps a test of collapse treatment could be made preliminary to insertion of the lucite spheres. The usual extrapleural stripping could be done and the space maintained with air for a few weeks. If the patient has negative sputum the collapse could be held by insertion of the lucite spheres; if the sputum remains positive

the procedure could be abandoned. The difficulty of maintaining the extrapleural space, the repeated needle punctures with possibility of contamination, and the inability to consider the negative sputum of a few weeks as a criterion of good results has caused the authors to decide against this method.

Since the plombage operation is not deforming patients more readily accept operative collapse and therefore it is possible to collapse earlier lesions than are obtainable for thoracoplasty. As the operation proves its effectiveness there will be a greater number of patients treated earlier in the course of their disease. Certainly the end results will then be increasingly better. The first patients in the present series were those with extensive disease and many with a questionable effective collapse on the opposite side produced either by thoracoplasty or pneumothorax. In the same series eight patients had bilateral collapse and 13 had either thoracoplasty or pneumothorax on the opposite side at the time of extrapleural lucite ball plombage.

When a patient persists with positive sputum after plombage it is usually difficult to determine the location of the active disease, although it is perhaps no more difficult than it is after thoracoplasty. As after thoracoplasty, physical examination, roentgenograms, laminograms, bronchograms, bronchoscopy and all available methods may not locate the source of the positive sputum. If the lesion is located under the lucite spheres, resection is the only treatment available at this time. This limited choice of treatment is a great disadvantage when compared with thoracoplasty, since disease under a thoracoplasty can be treated by revision thoracoplasty, open drainage, or resection.

CONCLUSIONS

1) Extrapleural lucite ball plombage has been used 72 times in 64 patients.

2) There have been two deaths, one postoperatively three days after operation from extensive flare-up of disease, and one from recurrent tuberculous meningitis several months after pulmonary plombage. No other complications have developed.

3) In 64 patients 54.7 per cent have negative sputa and none has been made worse. If the patients with bilateral disease are separated from those with unilateral disease the results are better. In 36 patients with unilateral disease 86.1 per cent have negative sputa. The patients have been followed six to 24 months after operation.

4) Factors are discussed that will undoubtedly bring about better end results.

5) Extrapleural lucite ball plombage has a definite place in the treatment of pulmonary tuberculosis and probably will be used more extensively in the future.

CONCLUSIONES

1) Se ha empleado el plombaje extrapleural con esferas de lucita 72 veces en 64 pacientes.

2) Han ocurrido dos muertes, una tres dias después de la operación, causada por una extensa propagación y, la otra, debida a meningitis tuberculosa recidiva varios meses después del plombaje pulmonar. No ha habido ninguna otra complicación.

3) De los 64 pacientes, el 54.7 por ciento tienen el esputo negativo y ninguno ha empeorado. Si se separan los pacientes con enfermedad bilateral de los que tienen enfermedad unilateral, los resultados resultan aún mejores. De 36 pacientes con enfermedad unilateral, el 86.1 por ciento tienen el esputo negativo. Se han observado a los pacientes de seis a veinte cuatro meses después de la operación.

4) Se discuten algunos factores que indudablemente causarán mejores resultados finales.

5) El plombaje extrapleural con esferas de lucita tiene un lugar bien definido en el tratamiento de la tuberculosis pulmonar y probablemente será usado más extensamente en el futuro.

REFERENCES

1 Overholt, R. H., Wilson, H. J., Szypulski, J. T. and Langer, L.: "Pulmonary Resection in the Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 55:198, 1947.

2 Bailey, C. P., Glover, R. P. and O'Neill, T. J. E.: "Comparison of Results in 200 Consecutive Resections for Pulmonary Tuberculosis," *J. Thorac. Surg.*, 18:36, 1949.

3 Brantigan, O. C. and Rigdon, H. L.: "Resection of the Lung in the Treatment of Pulmonary Tuberculosis," Accepted for publication by *Arch. Surg.*, 1949.

4 Brantigan, O. C.: "Thoracoplasty and Closed Intrapleural Pneumonolysis," *Am. Rev. Tuberc.*, 59:240, 1949.

5 Allen, J. V. and Kelly, C. W.: "End Results of Artificial Pneumothorax," *Am. Rev. Tuberc.*, 52:495, 1945.

6 Davison, R.: "Results of Thoracoplasty," *Dis. of Chest*, 12:431, 1946.

7 Kinsella, T. J., Mariette, E. S., Motell, P. M., Fenger, E. P. K., Fuenk, V. K., Larson, L. M., Cohen, S. S. and Neviec, F. C.: "Thoracoplasty in Treatment of Pulmonary Tuberculosis," *Am. J. Tuberc.*, 59:113, 1949.

8 Douglas, R.: "Late Results of Thoracoplasty," *Am. Rev. Tuberc.*, 56: 175, 1947.

9 Friedman, L. L., Davenport, L. O. and Bohorfousk, J. C.: "Extrapleural Pneumothorax," *Dis. of Chest*, 15:306, 1949.

10 Wilson, D. A. and Baker, Harold: "Experimental Surgical Pulmonary Collapse," *Surg., Gynec. and Obst.*, 82:735, 1946.

11 Wilson, David A.: "Use of Methyl Methacrylate Plombage in the Surgical Treatment of Pulmonary Tuberculosis," *Surg. Clin. North America*, 26:1060, 1946.

12 Wilson, D. A.: "Extrapleural Pneumonolysis with Lucite Plombage," *J. Thorac. Surg.*, 17:111, 1948.

13 Wilson, David A.: "Extrapleural Plombage," 1949, Personal Communication.

14 Grow, J. B. and Dwark, R. E.: "Extrapleural Pneumonolysis with Lucite Plombage," *Brit. J. Tuberc. and Dis. Chest*, 42:3, 1948.
15 Grow, John B.: "Use of Lucite Balls as a Filling after Extrapleural Pneumonolysis," Presented at National Tuberculosis Association and American Trudeau Society, Detroit, May 5, 1949.
16 Dolley, Frank S.: Discussion of Trent, J. C., Moody, James D. and Heatt, J. S., "An Evaluation of Extrapleural Pneumonolysis with Lucite Plombage," *J. Thorac. Surg.*, 18:173, 1949.
17 Trent, J. C., Moody, James D. and Heatt J. S.: "An Evaluation of Extrapleural Pneumonolysis with Lucite Plombage," *J. Thorac. Surg.*, 18:173, 1949.
18 Murphy, J. D.: Discussion of Trent, J. C., Moody, James D. and Heatt, J. S., "An Evaluation of Extrapleural Pneumonolysis with Lucite Plombage," *J. Thorac. Surg.*, 18:173, 1949.
19 O'Brien, E. J.: Discussion of Grow, John B., "Use of Lucite Balls as a Filling After Extrapleural Pneumonolysis," Meeting of the National Tuberculosis Association and the American Trudeau Society, Detroit, 1949.
20 Walkup, H. E. and Murphy, J. D.: "Extrapleural Pneumonolysis with Plombage," *Am. J. Surg.*, 78:245, 1949.

The Effect of Streptomycin on the Lesions of Tuberculous Meningitis

GEORGE I. OGURA, M.D. and JOHN DENST, M.D.*
Denver, Colorado

The extensive therapeutic use of streptomycin in tuberculous meningitis has necessitated the study of the effects of this antibiotic on the pathological processes of this disease. The conclusions of investigators concerning the alterations in the pathological picture in treated cases vary. Smith, Vollum and Cairns[1] found prolongation of the clinical course of the meningitis, but several of their cases exhibited complications in the form of hydrocephalus, old cerebral infarcts secondary to obstruction of small vessels, hypothalamic disturbances, and spinal fluid block. Of the 10 cases reported by Chiari,[2] some presented the lesions typical of untreated meningitis, others showed heavy white thickening of the meninges, and in one there was nodular meningeal calcification; severe hydrocephalus was usual. Organization of the exudate with meningeal scarring was typical, and obliterative endarteritis was an important finding. The observations of Cornil and collaborators[3] were similar. The case of Varga and Blasi[4] showed a fibroplastic basal exudate and hydrocephalus. Renth[5] noted arteritic lesions, including overgrowth of endothelium and obstruction of the lumen. Doniach[6] compared the vessels of 20 treated cases with those of untreated ones and consistently found productive arterial changes in those patients who had had a clinical course which was prolonged by the use of streptomycin. Fazio[7] ascribed the productive vascular reaction to the evolution of a chronic form of the disease. Baggenstoss, Feldman and Hinshaw[8] believed that streptomycin exerted an inhibitory or curative effect in meningeal tuberculosis. On the other hand, each of the three cases reported by Wright and Rees[9] showed hydrocephalus and a thick soft basal exudate that contained tubercle bacilli. Montgomery,[10] in a study of six cases, observed the persistence of progressive meningeal lesions while systemic tuberculous foci gave evidence of regression. Bornstein[11] believed that streptomycin was without effect on meningitis, but was responsible for healing of coexistent miliary tuberculosis.

We have had the opportunity to examine the brains from 10 fatal cases of tuberculous meningitis. Streptomycin had been ad-

*From the Department of Pathology of the National Jewish Hospital and the Department of Pathology of the University of Colorado School of Medicine.

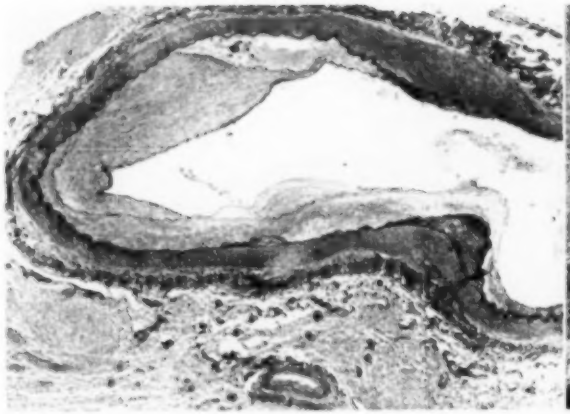


FIGURE 1

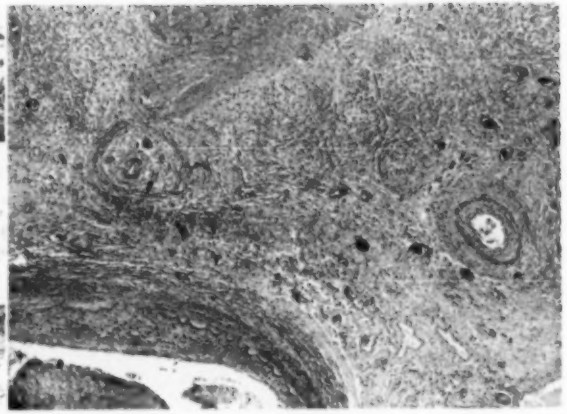


FIGURE 2

Figure 1: Basilar artery. Fibrous intimal proliferation and focal delamination of the internal elastic membrane. Elastic fiber-van Gieson stain. x35.—*Figure 2:* Fibrous meninges with tuberculoma in upper field and obstructed arterioles. A large artery at lower left shows productive intimal reaction and thinned media. Hematoxylin and eosin stain. x35.

ministered intramuscularly to all, and in addition it had been given by the intrathecal route to seven. Differences between treated and untreated cases were usual, particularly in the amount and character of the exudate and in the type of vascular lesion. Four representative cases summaries follow.

Report of Cases

Case 1: The patient, a white boy, three and one-half years of age, had had tuberculous meningitis for five months. One month after the initial symptoms, he received streptomycin in six-week courses which were separated by rest intervals of 10 days. Fifty mg. per kg. was given intramuscularly daily, and 50 mg. was given intrathecally every other day. Two months before death a complete spinal fluid block developed. Hyaluronidase (25 turbidity reducing units) was administered with each intrathecal dose of streptomycin during the last month, without effect. *Autopsy:* A primary complex containing tubercle bacilli and partly healed miliary tubercles in the lungs were present. The brain weighed 1210 grams. The brain stem and the interpeduncular area were coated with a thin, fibrous, opaque gray membrane; the arteries were inseparable from the membrane and showed diffusely thickened walls. A tuberculoma, 5 mm. in diameter, lay in a cortical sulcus neighboring the optic chiasm. The left globus pallidus contained a circumscribed cystic infarct, one cm. in diameter. The ventricles were not dilated. The cervical portion of the spinal cord was inseparably bound to the bony canal by fibrous adhesions. Two soft tuberculomas, each two and one-half cm. in maximum diameter, rested on the surface of the thoracic and lumbar portions of the spinal cord. *Microscopic:* The scanty exudate contained moderate numbers of lymphocytes, plasma cells, and a few epithelioid cells. Collagen fibrils and small patches of loose connective tissue were present throughout. Tubercle bacilli were identified. Hillocks and thick concentric, moderately cellular proliferations of intimal connective tissue narrowed the lumen of the larger arteries (Figs. 1 and 2). Mucinous material was observed between the collagen fibers. The plaques appeared to have been formed in successive layers. The internal elastic membrane showed only occasional focal splitting. The intimal plaques were covered by an elastic membrane but contained few delicate elastic fibrils. The media appeared normal. The adventitia was lightly infiltrated by lymphocytes. The cerebral and cerebellar cortex showed no tuberculous involvement.

Case 2: The patient, a white boy, eight years of age, developed tuberculous meningitis while being treated for tuberculosis of the hip. He was given two gm. of streptomycin intramuscularly and 75 mg. intrathecally every day for 50 days. After a rest period of one month, the intramuscular dose was again started, and the intrathecal dose was raised to 125 mg. daily for two weeks. He was discharged then, free of symptoms. Four months later the meningitis recurred, and he was hospitalized for a period of six months, during which time he received 24 injections of streptomycin intramuscularly in two gm. doses. Nine intrathecal doses of 75 mg. were also given. He was again discharged, but two weeks later a relapse occurred. A course of streptomycin similar to the previous one was again followed by a complete remission. One year later he had a final and fatal recurrence. Shortly before death a spinal fluid block developed, and

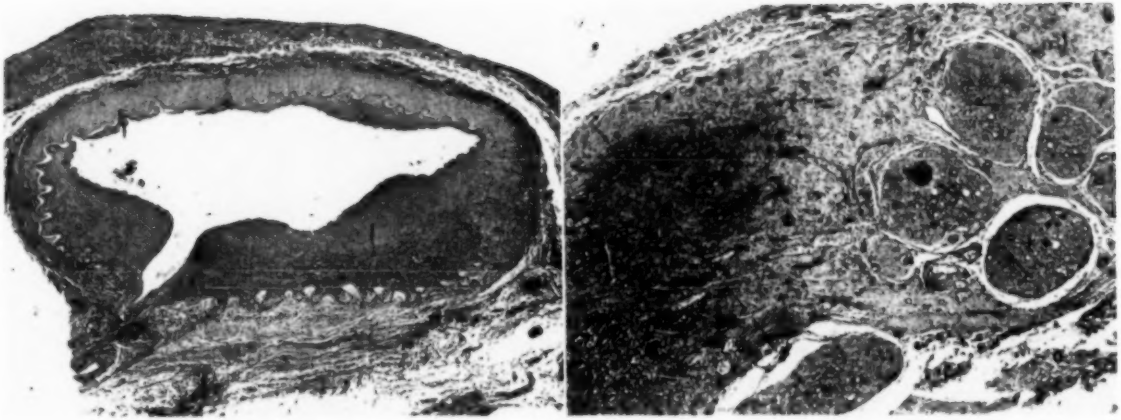


FIGURE 3

FIGURE 4

Figure 3. Middle cerebral artery. The lumen is partially obstructed by intimal collagen and the media is focally atrophic. Hematoxylin and eosin stain. x35.—*Figure 4*. Dense fibrosis of the meninges of the spinal cord. The collagen surrounds the nerve roots. It is organized by capillaries, and infiltrated by lymphocytes. Hematoxylin and eosin stain. x40.

heparin was injected intrathecally to no avail. The total duration of the course exceeded 25 months, and on three separate occasions he was clinically well, but at all times the spinal fluid contained cells and showed a low sugar level. *Autopsy:* The brain weighed 1325 grams. The ventral surface of the cerebellum, brain stem, and interpeduncular area was covered by a thin, tightly adherent, opaque gray membrane. The basilar and middle cerebral arteries exhibited severe thickening of the walls and extreme narrowing of the lumen. The ventricles were only slightly dilated, and the ependyma was transparent. A round perforation, one centimeter in diameter, was present in the septum pellucidum. An area of softening in the right globus pallidus measured 1.5 by 0.5 cm. *Microscopic:* The thin exudate contained moderate numbers of lymphocytes and a few Langhans' giant cells and tubercles. Fibrous connective tissue was widespread. The large arteries and the small branches within the cerebral and cerebellar sulci showed thick proliferations of intimal connective tissue which were composed of mature collagen fibers, scattered fibroblastic nuclei, and a few elastic fibrils on a blue mucinous background (Fig. 3). The internal elastic membrane was diffusely thickened, in isolated areas it was split into unequal layers, and in several vessels it was ruptured. The surface of each plaque was covered by an elastic lamina. At several points beneath the larger intimal masses, the media was atrophic and invaded by a few lymphocytes. The narrow adventitia was diffusely infiltrated by lymphocytes and a few histiocytes. The fibrotic arterioles were obstructed or obliterated. A single walled-off confluent group of necrotic tubercles was present on the posterior margin of the pons. The cystic softening of the globus pallidus contained a few gitter cells and capillaries.

Case 3: The patient, a Mexican female, two and one-half years of age, had tuberculous meningitis for three months for which she received daily intramuscular injections of streptomycin in one-half gram doses. *Autopsy:* The lungs and liver contained disseminated, partly healed miliary tubercles, and there was a mass of caseous hilar lymph nodes. The brain showed severe internal hydrocephalus. The leptomeninges, mainly in the basal region, were severely thickened and fibrous. Tubercle bacilli were identified in a smear of the meninges. The right basal nuclei were extensively softened. Hydrocephalus was severe. *Microscopic:* The leptomeninges were greatly thickened and contained heavy diffuse and patchy infiltrations of leucocytes, predominately lymphocytes. More or less discrete nodules, some of which contained Langhans' giant cells, were formed in some places. A few areas of caseation exhibited traces of calcification and a thick surrounding proliferation of fibroblasts mixed with lymphocytes. Both small and large meningeal arteries show considerable cellular and fibrous intimal thickening with subtotal obliteration of the lumen by the endarteritic process. Lymphocytic and fibrocytic nodules were seen beneath the ependymal lining, which was in part denuded. Lipoid phagocytes and proliferated capillaries comprised the softened area of the basal nuclei.

Case 4: The patient, a Japanese woman, 36 years of age, had tuberculous meningitis which ran a course of five and one-half months. Streptomycin was first given one month after the initial symptoms (total I.M. dose, 145 gm.; total I.T. dose, 1.35 gm.). Complete spinal fluid block occurred two and one-half months before death. *Autopsy:* The brain

weighed 1420 gms. The basal surface was covered by a thick, yellow, tightly adherent exudate. A cystic softening, 3 cm. in diameter destroyed the left putamen. The subarachnoid space of the spinal cord between the levels of T5 and T11 was obliterated by fibrous adhesions. Caudal to this segment the cord showed central softening. *Microscopic:* The spinal cord, the brain stem, and patchy areas of the cerebral cortex were covered by a sheet of dense collagen which was many times the width of the normal leptomeninges (Fig. 4). This tissue contained many capillaries and was infiltrated in some places by lymphocytes and occasional polymorphs. The adventitia of the arteries in all of these areas blended indistinguishably with the surrounding connective tissue. The media was focally compressed, and it was rarely invaded by lymphocytes. The intima showed advanced eccentric proliferations of dense connective tissue with evenly distributed fibrocytic nuclei. A few lymphocytes bordered the internal elastic membrane. The media of the arterioles was thinned due to stretching by a thick obstructive intimal growth of collagen. Encroaching on the choroid plexus in the lateral recess of the fourth ventricle was a walled-off, centrally necrotic mass of tubercles, which measured five millimeters in diameter. In the vicinity of the old infarct of the left putamen, a tubercle bordered a small artery.

Discussion

In the 10 cases, the duration of the clinical course of the meningitis was as follows: one month, five weeks, three and one-half months, four months, five months, five and one-half months, five and one-half months, seven and one-half months, 15 months, and 25 months. The age of the patient at the time of death varied from two years to 49 years. The duration of the course and the character of the lesions were apparently not related to the age of the patient. Hydrocephalus was severe in three cases, moderate in three cases, and slight in one. Cerebral softenings were present in four patients; three of these consisted of small old cystic infarcts of the lenticular nuclei, and the other was a large recent infarct of the basal ganglion. Small tuberculomas were encountered in the parenchyma of the brain in two instances, but in six cases discrete necrotic nodules, each about five millimeters in diameter, were present in the leptomeninges covering the brain stem or in the neighborhood of the interpeduncular area. In no case was there more than a minimal tuberculous involvement of the gray matter adjacent to the leptomeninx. Widespread non-specific degeneration of the nerve cells was more frequently observed, especially in the cases showing advanced hydrocephalus.

Of clinical importance was the development of obstruction to the flow of spinal fluid in four of the 10 patients, all of whom had received streptomycin intrathecally. The spinal cords of three of these patients were examined. Two had complete obstruction of the arachnoid space by tough fibrous adhesions, one at the level of T5 to T11, and the other in the midcervical area. The third,

who had extensive cavitary pulmonary tuberculosis with terminal meningitis lasting five weeks, showed a stringy fibrinous exudate coating the entire spinal cord. In an effort to overcome the effects of the block, three patients had been given hyaluronidase, heparin, or both intrathecally with the doses of streptomycin late in the course of the disease after the block had developed. This measure was without benefit. Another patient was given hyaluronidase prophylactically, and spinal fluid block failed to develop. Knowles[12] reported the occurrence of a block in an acute untreated case, which was explained by a thick soft exudate surrounding the cord. Four of the 16 treated patients of Smith and collaborators[1] had spinal fluid block, which in one case was transitory.

The translucent, necrotic, highly cellular exudate usually seen in untreated cases of tuberculous meningitis was not frequently observed. Rather, a thin, tough, shaggy opaque membrane without grossly visible tubercles covered the brain stem and interpeduncular area. Microscopically a decided tendency to fibrosis was noted. The stage of fibrosis varied: Some showed granulation tissue, and others contained small patches of hyaline tissue or a loose network of collagen fibers ramifying through the meningeal exudate. A thick coat of dense collagen, in which the nerve bundles and blood vessels were embedded, was also encountered about the brain and spinal cord. The most complete healing was seen in the case of a three-year-old girl who had had meningitis for 15 months, for which intrathecal therapy had been instituted within two and one-half months after the onset. A thin, noninflamed fibrous membrane covered the brain stem; death was due to extreme hydrocephalus caused by a thick fibroblastic mat which covered the floor of the fourth ventricle and obstructed the foramina. In most cases the cellular component was moderate in amount, with a predominance of lymphocytes and only a few epithelioid and multinucleated giant cells. Exceptions were two cases in which focal necrosis and pleomorphic cellular infiltrates were prominent; both received streptomycin solely by the intramuscular route.

The gross appearance of the arteries was sometimes normal, but often there was severe, firm, white thickening of the wall with extreme narrowing of the lumen. The microscopic arterial lesions were impressive. The intima was thickened, sometimes concentrically, but often to a greater degree in one area than another; the lumen was narrowed but never obliterated. The intima was composed of mature collagen fibers with moderate numbers of evenly dispersed fibroblastic or fibrocytic nuclei. In the sections stained by hematoxylin and eosin, pale to dark blue mucinous material frequently was seen between the connective tissue fibers. In the advanced cases, only rarely did a few lymphocytes or mon-

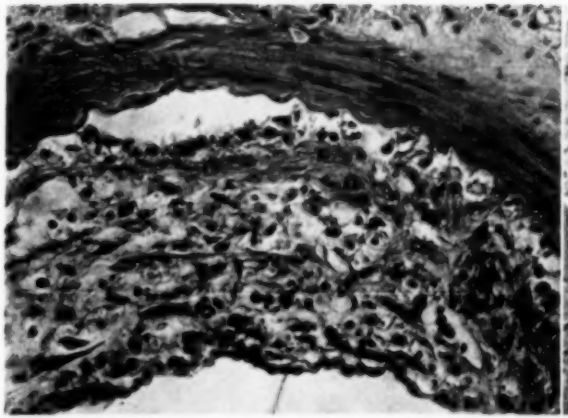


FIGURE 5

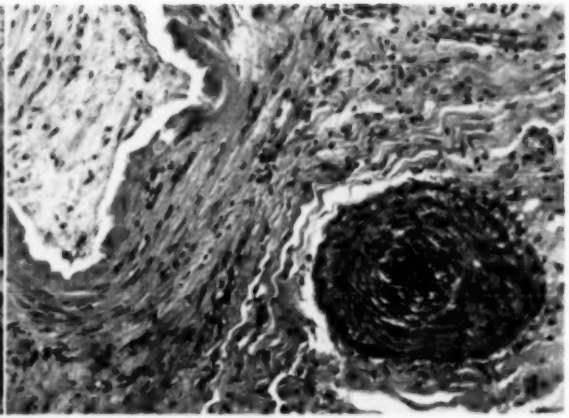


FIGURE 6

Figure 5: The cerebral artery with fibrotic intima at right is embedded in collagen. A thick-walled obstructed arteriole is present in the upper left part of the field. Hematoxylin and eosin stain. x175. — *Figure 6:* Small cerebral artery: Mononuclear cells are mixed with an edematous proliferation of intimal fibroblasts. Hematoxylin and eosin stain. x325.

onuclear cells invade the intima, and these were present in the peripheral portion near the media. The internal elastic membrane was unchanged, diffusely thickened, or focally thinned; it was occasionally ruptured. In short segments it was split into several uneven layers, and a few delicate elastic fibrils were sometimes present in the intimal connective tissue. A subendothelial elastic band on the luminal surface of each plaque merged with the internal elastic membrane at the margins of the thickening. The media was intact for the most part, but in some places it showed compression atrophy, edema, or slight infiltration by lymphocytes. The adventitia was the only coat of the vessel consistently to show active inflammation, being invaded by the same type of cells which were present in the contiguous meninges. In some cases the adventitia blended imperceptibly with the adjacent connective tissue. The walls of the arterioles exhibited all degrees of thickening, the lumens were severely obstructed (Fig. 5), and leucocytic infiltration of the wall was not uncommon. Venous thrombosis was not encountered, and alterations in the wall of veins were not prominent.

This productive intimal reaction appeared identical with that described by Chiari,[2] Doniach,[6] and Fazio.[7] The presence of vascular lesions, particularly those of the arterioles, are of importance because the parenchymatous softening may be attributed primarily to them. In some untreated cases we have seen fibrous intimal proliferations and fibroblastic masses filling the lumen, but these were intermixed with leucocytes or were associated with perivascular necrosis. Henschen[13] observed filling of the arterial lumen by fibrous tissue in untreated cases. Winkelman and Moore[14] detailed five cases, in a series of 200 untreated patients, which showed similar fibrotic intimal lesions. They also described subendothelial inflammatory infiltrates, which were sometimes verrucose and occasionally contained tubercles. Concentric intimal fibrosis, closure of the lumen, leucocytes in the intimal connective tissue, caseation of the intima and wall, and the fibrinoid-hyaline change of Askanazy were encountered. Instead of showing this variety of lesions, our treated cases presented a somewhat stereotyped picture, with the productive feature dominant. Panarteritis and necrosis were limited to arterioles, intimal tubercles were not seen, and thrombosis was absent. Two treated cases of short duration did exhibit a more acute type of inflammation; in one the endothelium was lifted by accumulation of mononuclear cells, and in the other lymphocytes and mononuclear cells were numerous in a loose edematous network of intimal fibroblasts (Fig. 6). These lesions are not specific. They may simulate Heubner's luetic endarteritis, and we have seen the same reaction in a case of chronic menin-

gitis which followed the removal of a brain tumor. The pulmonary arteries neighboring tuberculous foci frequently appear similar.

The arterial inflammation results from encroachment of the exudative reaction in the meninges on the vessel wall. Whether the productive component is due to the lengthening of the course of the disease or is a result, in part, of a local irritative action by the streptomycin cannot be stated with certainty. Both Doniach[6] and Zollinger[15] found no evidence that streptomycin had any direct effect on the vessels, and the fact that the same process occurs in untreated cases substantiates this conclusion. However, in our cases there appeared to be a difference in the degree of the fibrosis, both in the meninges and arterial intima, between those treated exclusively by the intramuscular route and by this method combined with intrathecal therapy. Invariably those given prolonged courses of intrathecal streptomycin showed widespread intimal fibrosis, and it was in these patients that obstructive adhesions of the spinal canal occurred. It is possible that higher concentrations of the drug were obtained with intrathecal therapy, and therefore "healing" was more advanced. In four of the five cases studied bacteriologically at autopsy, tubercle bacilli were identified in the meninges or in the center of small walled-off tuberculomas. It appeared likely that bacilli lurking in such foci, inaccessible to the drug, might be the source of reseeding of the meninges when therapy is interrupted. Zollinger[15] stated that in only four of 22 cases was there complete healing of caseous foci and absence of organisms. He believed that streptomycin was of use through its bacteriostatic action, but that success in treatment still depends on the resistance of the body.

SUMMARY

The pathological findings in the central nervous system of 10 fatal cases of tuberculous meningitis are presented; all patients had received streptomycin therapy. The clinical course was prolonged up to 25 months. Acute inflammatory lesions in the leptomeninges showed regression except in the cases of short duration, and all degrees of fibrosis was observed. In general the arteries exhibited extensive intimal fibrosis and narrowing of the lumen, while the arterioles were severely obstructed or infiltrated by leucocytes. Obstructive adhesions about the spinal cord caused spinal fluid block in four patients who were treated by the intrathecal route. Internal hydrocephalus was a common complication, even in cases where the acute meningitis was largely healed. Infarction of the basal nuclei was not infrequent and could be ascribed to the vascular lesions. Tubercle bacilli were identified in

the meninges and in small meningeal tuberculomas in patients who had received large doses of streptomycin.

Addendum: Since the completion of this study a report by Winter entitled "The Effect of Streptomycin upon the Pathology of Tuberculous Meningitis" was published in The American Review of Tuberculosis, 61:171-184, 1950, which described the reparative process in tuberculous meninges, the proliferative endarterial reaction, and the complications.

RESUMEN

Se presentan los hallazgos patológicos en el sistema nervioso central de 10 casos fatales de meningitis tuberculosa. Todos los enfermos se habian tratado con estreptomicina. La evolución clínica se habia prolongado hasta 25 meses. Las lesiones agudas inflamatorias habian sufrido regresión excepto en los casos de corta duración, se observaron todos los grados de fibrosis.

En general las arterias mostraban fibrosis extensa de la íntima y estrechamiento de la luz, en tanto que las arteriolas estaban obstruidas fuertemente o infiltradas con leucocitos. Las adherencias alrededor de la médula causaron bloqueo de líquido en cuatro enfermos tratados por la vía intratecal.

La hidrocefalia interna fué una complicación común aún en los casos en que la meningitis aguda estaba curada. El infrato de los núcleos basales no era poco frecuente y podría atribuirse a las lesiones vasculares. Se identificaron bacilos de la tuberculosis en las meninges y en pequeños tuberculomas meningeos en enfermos que recibieron grandes dosis de estreptomicina.

REFERENCES

1 Smith, H. V., Vollum, R. L. and Cairns, H.: "Treatment of Tuberculous Meningitis with Streptomycin," *Lancet*, 1:627, 1948.
2 Chiari, H.: "Pathologisch-anatomische Befunde bei mit Streptomycin behandelten Fallen von Meningitis tuberculosa," *Wiener Klin. Wochenschr.*, 60:837, 1948.
3 Cornil, L., Mattéi, Ch., Gastaut, H. and Payan, H.: "Considérations anatomiques sur les méningites tuberculeuses prolongées de l'adulte traitées par la streptomycine," *Le Concours Médical*, 71:683, 1949.
4 Verga, P. and Blasi, A.: "Rilievi anatomo-patologici in un caso di meningite tubercolare trattato con streptomicina," *Archivio di Tisiologia*, 2:640, 1947.
5 Renth, M.: "A Case of Tuberculous Meningitis Treated with Streptomycin," *Med. J. Australia*, 2:549, 1948.
6 Doniach, I.: "Changes in the Meningeal Vessels in Acute and Chronic (Streptomycin-Treated) Tuberculous Meningitis," *J. Path. and Bact.*, 61:253, 1949.
7 Fazio, C.: "Osservazioni cliniche ed anatomopatologiche su di un caso di meningite tubercolare trattato con streptomicina," *Revista di Patologia nervosa e mentale*, 69:1, 1948.
8 Baggenstoss, A. H., Feldman, W. H. and Hinshaw, H. C.: "Effect of Streptomycin on the Pathology of Generalized Miliary and Meningeal Tuberculosis," *Proc. Staff Meet., Mayo Clin.*, 22:265, 1947.
9 Wright, G. P. and Rees, R. J. W.: "Brain from Streptomycin-Treated

Cases of Tuberculous Meningitis." *Proc. Roy. Soc. Med.*, 41:456, 1948.
10 Montgomery, G. L.: "Streptomycin in Tuberculous Meningitis in Childhood: The Pathological Findings in Six Fatal Cases," *Glasgow Med. J.*, 29:235, 1948.
11 Bornstein, P. K.: "Streptomycin in Miliary Tuberculosis with Tuberculous Meningitis," *Quart. Bull., Sea View Hosp.*, 8:219, 1946.
12 Knowles, E.: "Tuberculous Meningitis with Paraplegia as the Dominant Feature," *Brit. Med. J.*, 2:686, 1949.
13 Henschen, F.: "Encephalomalacia on Tuberculous Basis," *Acta. Med. Scandanavica*, 50:56, 1932.
14 Winkelman, N. W. and Moore, M. T.: "Meningeal Blood Vessels in Tuberculous Meningitis," *Am. Rev. Tuberc.*, 42:315, 1940.
15 Zollinger, H. U.: "Die Streptomycin-behandelte Meningitis Tuberculosa und Miliartuberculose," *Schweizerische Z. für Pathologie und Bacteriologie*, 12:176, 1949.

Streptomycin and the Thoracoplasty Patient*

ELLIOTT MICHELSON, M.D.†
Baltimore, Maryland

Streptomycin has been shown to be a valuable drug in the treatment of pulmonary tuberculosis; but it is not a definitive form of therapy and should be considered mainly as an adjuvant to such modalities as bed rest, collapse therapy and resection surgery. The major problems confronting both the phthisiologist and the surgeon are the type of pulmonary disease most likely to benefit from streptomycin, its most effective dose and duration, and the final results accomplished by the integration of the drug with associated therapeutic procedures. In the initial stage of tuberculous infection, the viable exudate is predominantly polymorphonuclear neutrophils. At this stage of the lesion, streptomycin may help to completely absorb the disease process. Within the exudative lesion there may be small areas of necrosis, which do not liquify, cannot be evacuated, have no blood supply, and upon which streptomycin has little effect. Medlar[1] has shown that tuberculosis endobronchitis is always associated with peripheral necrotic pulmonary lesions and that the type of bronchial lesion depends upon the nature of the continued bacterial contamination and the local reaction to this noxious material. Since the bronchial lesions are primarily exudative, and the drainage of necrotic material adequate, streptomycin should be and is of value in healing the mucosal lesions, although it cannot reverse destructive changes in the bronchial wall. The value of streptomycin in arresting the disease process will, therefore, depend upon the type of parenchymal and bronchial lesions.

In the past three years, 50 patients were treated at Sunmount Veterans Administration Hospital with streptomycin and thoracoplasty. At the beginning, prior to protocols allowing adjuvant treatment, all patients were treated for 120 days without surgery, but later when resistance was found to occur in approximately 50 per cent of cases after 42 days and 70 to 90 per cent in 120 days of streptomycin therapy, an attempt was made to integrate the use of the agent with the surgical procedures. These cases, on analysis, are found to fall into three main groups:

*Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author is the result of his own study and does not necessarily reflect the opinion or policy of the Veterans Administration.
†Formerly Chief of Surgery, Veterans Administration Hospital, Sunmount, New York.

1. Prophylaxis,
2. Combined Therapy,
3. Operative Complications.

Group 1: Prophylaxis: Twenty-two patients were given streptomycin prophylactically with thoracoplasty, by reason of their being on an alternate case protocol (Table I). Streptomycin was given one to three days prior to, and 14 days after, each thoracoplasty stage; 1.0 or 1.8 grams per day for 26 to 120 days. There were no spreads of disease. One patient developed a small pleural effusion after a second stage, which absorbed in a short time without event, and another developed a hazy shadow in a lower lobe that cleared in less than a month. Eight of the nine acute cases in this series are clinically well 12 to 28 months after thoracoplasty; the ninth left the hospital against advice three months after surgery and suffered a spread of disease five months later. Poor results were obtained in three patients, and, in each instance, the cavities did not close; one is living with his disease; one had a spread 12 months after operation; and one had a lobectomy nine months after thoracoplasty with subsequent contralateral spread four months later. In reviewing the results of streptomycin prophylactic therapy with thoracoplasty at all Veterans Administration Hospitals by the Streptomycin Conferences (Table II) it was found that there were 2 per cent spreads in 355 cases given streptomycin and 3 per cent spreads in 295 cases treated without this drug.[2] It can, therefore, be inferred that the routine use of streptomycin with thoracoplasty is of questionable value.

Group 2: Combined Therapy: This group consists of severely ill patients who were given streptomycin in order to arrest the pro-

TABLE I

Prophylactic Use of Streptomycin with Thoracoplasty

Indications for Streptomycin:		
Progressive Disease	13	
Acute Disease	9	
Total Cases		22
Results:		
Good	18	
Poor	4	
Deaths	0	
Poor Results:		
Cavity open 12 months after Thoracoplasty		
Spread 12 months after Thoracoplasty		
Spread 4 months after Lobectomy		
Spread 8 months after Thoracoplasty		

TABLE II

V. A. Streptomycin Conference (1948-49)—Surgical Prophylaxis

	No. of Patients	No. of Operations	Sput. Conv., Cult. or G.P.	Spreads	Fistula	Empyema	Wound Infection	DEATHS — Operation	DEATHS — Non-Operation
			Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
Thoracoplasty:									
1. Streptomycin treated	355	859	97	2	0	1	2	0	1
Not treated	295	736	43	3	0	1	2	2	0
Lobectomy:									
3. Treated, without previous streptomycin	147	170	70	7	3	2	4	3	1
4. Treated, with previous Streptomycin	120	1 25	35	14	10	7	6	5	1
Pneumonectomy:									
5. Treated, without previous streptomycin	103	125	73	7	6	6	8	9	4
6. Treated, with previous streptomycin	67	75	54	11	8	12	12	13	10

gress of their disease and bring them into a better host-parasite equilibrium so that collapse therapy might be possible. These cases may further be subdivided into three series:

A. Streptomycin resistant cases.
B. Streptomycin course followed by remission, then streptomycin and thoracoplasty.
C. Streptomycin course, collapse without streptomycin.

Series A: There were 15 streptomycin resistant cases who had thoracoplasty operations one to eight months after antibiotic therapy (Table III). The indications for streptomycin were far advanced bilateral unstable disease in four, severe spreads in eight, marked toxicity in two, and tuberculous empyema in one. Streptomycin in doses of 0.5 grams, twice a day for 120 days, was given, and two had two courses. No patient received streptomycin during the operative period. They were all severely ill; 10 had acute disease and the rest had pneumonic type of lesions. The cavities averaged 4 cm. in diameter and all but four were thick-walled. Seven of the 15 had anterior stages first, and four of these were followed by Monaldi drainage and subsequent thoracoplasty. In the immediate post-operative period, there were seven spreads: one after an anterior, four after a first stage, and one after a second stage of thoracoplasty. The final results 12 to 24 months after surgery were good in five, fair in eight, and two died. One patient spread after the first stage and died of a pulmonary em-

TABLE III

Streptomycin Resistant Cases Subjected to Thoracoplasty

Indications for Streptomycin:		
F. A., unstable	4	
Spreads, severe	8	
Toxic	2	
Empyema, Tuberculosis	1	
Total Cases		15
Complications after Thoracoplasty:		
Immediate:		
Spreads	7	
Sinus tract	1	
Late:		
Spreads	2	
Results:		
Good	5	
Fair	8	(7 with open cavities)
Deaths	2	Embolus 26 days post-operative Tuberculous meningitis 1 week after pleuropneumonectomy

bolus to the contralateral lung 26 days later. The other death occurred in a patient with tuberculous empyema and bronchopleural fistula, whose thoracoplasty was followed by pleuropneumonectomy, with death one week later from miliary and meningeal tuberculosis. Of the eight cases listed as fair, seven had uncollapsed cavities. All the patients in this series were poor risk cases; the good results occurred in only 33 per cent, but the remaining living cases, while not arrested, are definitely improved. The incidence of spreads is high, but in view of their unstable pre-operative course, one cannot deny that they might have been just as high without surgical intervention.

Whether or not drug resistance of bacillus can be correlated with decreased resistance of the host cannot be answered by this group of patients, since they are by design a highly selected group. It is our impression that streptomycin resistant patients tolerate collapse or resection poorly. The results of the Veterans Administration streptomycin studies show the incidence of complications to be much greater in patients who had streptomycin prior to resection than those who were first given this drug at the time of operation (Table II). Although no adequate studies of streptomycin resistance were made in the V. A. series, it would suggest that the presence of drug resistance is responsible for the increment of complications.

Series B: There were 10 patients treated with streptomycin because of severe spreads, who, one to eight months later, while still sensitive to the drug and revealing no improvement or remission, were treated with thoracoplasty together with another course of the drug (Table IV). These patients received 1.0 to 1.8 grams of

TABLE IV

Streptomycin Sensitive Cases Treated with Streptomycin and Thoracoplasty

Cases: 10		
Complications:		
Pleural Effusion	1	
Pulmonary Embolus (?)	1	
Spreads	3	
Results:		
Good	4	
Fair	3	(Cavity Open—Sputum Positive)
Deaths	3	Pneumonectomy Hemorrhage 5 months later Hemorrhage 12 months later

streptomycin for 55 to 120 days at first, and during surgery were given 1.0 grams per day for 42 to 86 days. In the early postoperative period, there were three spreads and one of these died five months later of hemorrhage. One patient had a small pleural effusion, which absorbed within a month, and 19 days after his second stage presented suggestive evidence of pulmonary embolus which was treated with dicoumarol, with no subsequent complications. There were four good results with cavity closure and negative sputum on cultures 12 to 20 months after operation. Three are living with open cavities and three died. Two of the deaths were due to hemorrhage five and 12 months, respectively, after operation, and one died from right heart failure following pneumonectomy. In resumé, it might be stated that all these cases were of the acute progressive type; that streptomycin did not appear to prevent spreads even though the bacilli were sensitive, and that further progression of disease appeared to be stopped, provided there was closure of the cavity.

Series C: There were three cases who had been treated with streptomycin for progressive, acute disease, and, although the bacilli remained sensitive, thoracoplasty was performed at a later date without the drug. One patient had a slight increase six months after streptomycin; thoracoplasty was performed with good results 12 months later. Another continued to have an open cavity after two courses of streptomycin and thoracoplasty closed the cavity with good results 15 months after surgery. The last case is of sufficient interest to be reported in more detail:

This 30 year old colored male was admitted to Sunmount Veterans Administration Hospital in June 1946, with the history of acute onset one month prior. He had an opaque cavitated right upper lobe and scattered infiltration in the left mid-zone region. He was placed on bed rest for two months; streptomycin was then given, 1.8 grams per day for 120 days with symptomatic improvement, clearing of the left lung lesion, and moderate decrease of infiltration with contraction in right upper lobe, but without cavity closure. In April 1947, further activity was seen on the left and he was given another course of streptomycin, 1.8 grams for 60 days. No further change in the x-ray shadows was seen and two and one-half months later, a two stage seven-rib thoracoplasty was performed without complications or streptomycin therapy. His organisms were streptomycin sensitive. His sputum, prior to operation, was positive on culture, and following collapse therapy became negative. Nine months after completion of thoracoplasty, he began to lose weight, suffered anorexia, ran low-grade fever, and developed right submaxillary swelling. On September 3, a caseous necrotic tuberculous lymph node was resected, with secondary closure five days later and primary healing. Sputum became positive on culture in August, concentrates were positive in October, and in November a cavity beneath the collapsed portion of his chest was noted on planigrams. Three weeks later, or 13 months after thoracoplasty, another

spread or reactivation was noted on the left and patient was placed on complete bed rest with streptomycin and para-aminosalicylic acid.

This case illustrates that streptomycin, and possibly other chemotherapeutic agents, may diminish or arrest the progress of disease, but, in the absence of natural immunity, no lasting benefits may accrue. Moreover, it might suggest that one must accept early good results in thoracoplasty on patients with streptomycin "stabilized" lesions with caution.

Group 3: There were seven patients who developed spreads during thoracoplasty who were then given streptomycin. There were four cases with acute, progressive disease, and, in three the final results were good; the failure occurring in a patient who left AWOL three months after operation and developed contralateral cavitation one year later. In the three chronic cases, two of the spreads were associated with broncho-pleural fistula, with good results in all. The drug was given seven to 13 days after spread was noted; 1.0 to 1.8 grams per day for 25 to 66 days, and allowed completion of thoracoplasty in six of the cases. It is evident that streptomycin will give temporary help in allowing the stages of thoracoplasty to proceed.

DISCUSSION

From this small series, impressions rather than conclusions may be stated. It appears that streptomycin alone is of little value in the preparation of chronic, stable disease for collapse procedures. The use of streptomycin in acute early tuberculosis may render surgery feasible, although final results will not be as satisfactory as in the stable chronic case that receives no streptomycin. In cases with recent spreads, but in otherwise stable lesions, streptomycin may allow early operation with good results, providing cavity closure is achieved. If cavity closure is accomplished, it is our opinion that arrest of the disease process may obtain in a large percentage of the cases. Streptomycin should not be used longer than is necessary, since it may be of value for treatment of reactivated disease or for further surgery at a later date.

The decrease of toxicity, and of the amount and bacterial content of sputum, allows the tuberculous patient to be operated upon earlier and with less hazard. However, the clearing of x-ray shadows during and following streptomycin therapy should not be accepted as of the same biologic significance as roentgenographic clearing that follows bed rest. Pre-necrotic lesions may resolve to a great extent under the influence of streptomycin; however, necrotic foci are not greatly influenced and their presence affords the hazard for future exacerbation of the disease. The case cited illustrates the principle that temporary arrest of disease with streptomycin and adequate surgical intervention do not confer

lasting benefits in the absence of natural resistance and immunity.

In surgical practice, therefore, the main value of streptomycin therapy is in the treatment of non-necrotic lesions prior to surgery, and in spreads following thoracoplasty. In the acutely ill patient, the chief value of streptomycin therapy is that the patient may recover sufficiently to permit surgery, and in such cases a definitive surgical program should be envisioned prior to the use of streptomycin, with an appreciation that the final results may not equal those anticipated in patients capable of stabilizing their disease without the splint of streptomycin.

DISCUSION

Con esta serie pequeña, se pueden obtener impresiones, en vez de conclusiones. Parece que la estreptomicina sola, no tiene gran valor en la preparación del enfermo crónico, estable, para la colapsoterapia. El uso de la estreptomicina, en los casos agudos de tuberculosis, puede hacer la cirugia posible, aunque no se obtendrá tan bien resultado, como en los casos crónicos y estables, sin estreptomicina. En Casos con reciente diseminación, por otra parte, lesiones estables, la estreptomicina prepara el terreno para una cirujia precoz, con bien resultado, siempre que la cavidad se cierre. Si el cierre de la cavidad se obtiene, es nuestra opinion que se controlara la enfermedad en la gran mayoria de los casos. La estreptomicina no debe usarse mas tiempo que lo necesario, desde el momento que puede ser de gran valor en caso de reactivación de la enfermedad, o en caso de que cirujía sea necesaria mas tarde.

La desminución de la toxicidad, la cantidad de esputos, y del contenido de bacilos en los esputos, en los enfermos de tuberculosis, hace que los enfermos puedan ser operados mas precozmente y con menos peligro. Sin embargo la clarificación de los sombras en la radiografía, durante y después del tratamiento con estreptomicina, no deben considerarse los mismos que las que se obtienen después de tratamiento de reposo o procedimientos de colapsoterapia, tales como la toracoplastía. Parece que una lesion prenecrosante, puede resolverse hasta cierto punto con la estreptomicina, sin embargo, un foco necrótico no será influenciado grandemente y su presencia puede causar exacerbación de la enfermedad. El caso citado, demuestra el principio, que el arresto temporario de la enfermedad con estreptomicina y con una intervención quirúrgica adecuada no da un resultado duradero, si no una resistencia natural e inmunidad.

En la práctica quirúrgica, entonces el mayor valor de la estreptomicina es en el tratamiento de las lesiones que no son necrosantes, antes de la operación y en diseminación después de la toracoplastia. En el enfermo agudo, el mayor valor de la estreptomicina es, que

el enfermo se mejora lo suficiente como para permitir la operación, en tales casos un plan quirúrgico definitivo, debe de ser visualizado antes de empezar el tratamiento con estreptomicina; apreciando el hecho de que talvez el resultado no será igual al que podria esperarse en enfermos capaces de estabilizar sus lesiones sin la ayuda de la estreptomicina.

REFERENCES

1 Medlar, E.: "Personal Communication."
2 Minutes of the Seventh Streptomycin Conference, V.A., April 1949.

Pneumonectomy in a Case of Loeffler's Syndrome

MAURICE G. BUCKLES, M.D., F.A.C.S., F.C.C.P.*
and EDWARD C. LAWLESS, M.D.
Columbus, Ohio

William Loeffler, Professor of Medicine at the University of Zurich, in 1932, reported a group of cases of "special forms of pneumonia" while discussing the differential diagnosis of pulmonary infiltrations. Emphasis was placed on the importance of defining "quickly disappearing shadows which do not correspond to any special nosologic entity." Special note was also made of the fact that some forms of pneumonia were present with few symptoms.

Etiology: A multitude of theories have been offered as to possible etiology of Loeffler's syndrome without any definite conclusions. A combination of some of these etiological factors may be present in any given case which again makes the issue more complicated.

1) Originally Loeffler's syndrome was thought to be a benign form of tuberculosis or tuberculid, i.e., a reaction of the lungs to the products of the tubercle bacillus. In subsequent series of cases, sufficient negative tuberculin tests were found to disprove this theory.

2) Parasitic theory has been advocated by various investigators following the isolation of common parasites from their patients with the findings of Loeffler's syndrome, such as amoebiasis,[2] trichinosis,[3] brucellosis,[4] ascarides,[5-7] Necator Americanus,[8] and other less frequent parasitic infestations have been reported. Alphers[9] includes the parasites in his classification as the intrinsic group (associated with infection) and explains the pathogenesis on an allergic basis. Plant pollen, as an etiological factor, belongs in the extrinsic group as reported by Engel.[10]

3) Allergic theory, which has had many advocates especially during the more recent years, is based on the fact that antigen-antibody interaction is thought to result in the liberation of a histamine-like substance which causes an increase in vascular permeability and eventually generalized edema. This edema has been shown to be responsible for the production of the clinical symptoms of allergy; in cases of Loeffler's syndrome, the lung

*Assistant Professor Thoracic Surgery, Ohio State University and Attending Thoracic Surgeon, Franklin County Tuberculosis Hospital, Columbus, Ohio.

infiltration, as demonstrated in the roentgenogram, may represent a hyperergic form of response in which the interalveolar capillaries, the larger vessels and the associated mesenchymal structures participated. These smaller blood vessels or interstitial tissue of the lung[12] have been termed the basic "shock tissue" rather than the bronchi as in true asthma. The resultant interstitial edema[11] or angioneurotic edema[13] and cellular infiltration could possibly account for the roentgenologic picture. This "allergic edema" has been likened to urticaria with the exception that the involvement is centered in the alveoli. The antigen involved in this proposed antigen-antibody reaction may vary in individual cases, e.g. bacteria, toxins, virus or even plant pollen (Privet).[10] As has been shown, most cases develop during July and August and possibilities of seasonal antigens becomes of greater importance. Sunlight,[14] in itself, has been suggested as a possible etiological factor.

Hansen-Pruss and Goodman[15] discuss the problem in a slightly different manner, inasmuch as mesenchymal and endothelial tissue can become sensitized and react in an allergic manner on subsequent contact with an offending allergen. Tissue can become sensitized to bacterial products, whether they be protein or carbohydrate in nature. A person with frequent respiratory infections becomes sensitized to one or a group of bacteria and then shows an allergic response of the pneumonic type of reaction upon subsequent contact. Differentiation of an allergic infiltration, as in Loeffler's syndrome, from bacterial pneumonitis, as in lobar pneumonia, is based on absence of fever, mild toxicity and character of the sputum.

Harkavy[11] has shown in pathological sections and biopsies that the severe non-fatal cases of Loeffler's syndrome, showed changes in the blood vessels varying from intimal thickening to necrotizing arteritis with a perivascular eosinophilic infiltration, almost indistinguishable from periarteritis nodosa. In asthma due to the usual allergens, the complication of a bacterial hyperergy may cause a disease much less benign than that usually associated with Loeffler's syndrome. The presence of transient lung infiltration with eosinophilia in such cases may be a warning of a generalized vascular allergy with panarteritis as an eventual outcome.

4) In a miscellaneous group of etiological factors Von Meyenburg[7] states that Loeffler's syndrome may simply be an eosinophilic pneumonia. The occurrence of foci of eosinophilic infiltration in organs distant to the lungs would lead one to believe this to be a hematogenous manifestation of a pre-existing condition. The possibility that Loeffler's syndrome may be due to a virus infection in an essentially allergic person is considered. Infiltration in the

lungs due to localized atelectasis without giving a cause for this atelectasis has also been postulated as a cause. Selective reaction of the interstitial tissue likewise is a vague description of a possible etiological factor. Lung emboli, pulmonary infarcts, localized asthma have been mentioned as possible etiological factors.

The literature is scant for accurate description of pathology in Loeffler's syndrome. Von Meyenburg[7] performed autopsies on four patients with Loeffler's syndrome who died during their illness from other non-related causes. Harkavy[11] likewise reports four deaths and Bayley, et al[16] presented the pathological findings in one. As far as can be determined from literature, the authors' case is the first operative specimen reported. In all, there is a consistency in the pathological findings both with the gross and microscopic descriptions.

Grossly, the appearance of the pulmonary foci are not characteristic. They resemble focal pneumonias of varying forms, size and distribution. Pleura thickening over these regions and numerous adhesions were frequently found. Cut section revealed these nodular regions to be grayish yellow and firm to palpation and no exudate could be expressed. Pulmonic infiltration may consist of dark red consolidated regions, usually at the bases which exude serum and blood. The bronchi may contain mucus, and the walls may be quite thickened. Alveoli may be quite dilated. Microscopically eosinophilic infiltration is seen in the interaveolar septae of the lungs; endarteritis obliterans of the pulmonary vessels; diffuse eosinophilic infiltrations in the heart muscle, the intestine, and the abdominal muscle; diffuse involvement of the small medium sized arteries in various organs, including such changes as intimal thickening, infiltration with many eosinophilic leukocytes, endarteritis obliterans, necrotizing arteritis and periarterits. Sections from the firm scar-like regions described[23] revealed extensive replacement of the normal parenchyma of the lung by groups of fibroblasts and collagenous fibers. In the latter there are large numbers of eosinophiles, plasma cells, lymphocytes and giant cells.

Symptoms: The clinical picture of any disease is a composite of many factors and depending on the individual factors that make up the clinical entity, classification of the disease is determined. Certain diseases have specific pathognomonic features that identify them immediately; whereas, in others the presenting factors are varied to the extent that the clinical entity is not clear cut. Consequently, accurate differential diagnosis is necessary to come to a definite conclusion. Such is the case in the syndrome of transient pulmonary infiltration with blood eosinophilia.

Various authors have reported many symptoms presented in Loeffler's syndrome; some cases present all the symptoms while

others have practically an asymptomatic course. Routine physical examinations including roentgenological inspection have disclosed a number of the reported cases.

Symptoms most commonly found in Loeffler's syndrome are:

1) Generalized weakness or fatigue. 2) Nausea. 3) Slight fever. 4) Cough, may be dry or productive. 5) Headache. 6) Pain in chest. 7) Dyspnea. 8) Loss of weight. 9) Wheezing or asthmatic-like breathing. 10) Diarrhea. 11) Photopsia.

Physical Signs: One of the differential characteristics of Loeffler's syndrome is the paucity of conventional signs as compared to the x-ray shadows. A battery of physical signs has been described but rarely do many of them appear simultaneously. Saslow[17] et al, state "The clinical picture is so benign that diagnosis of it renders the necessity for heroic treatment unnecessary." This is not always true[16] but is significant in explaining the lack of physical findings in most cases. The customary findings are: slight impairment of percussion note over the lesion; occasional crepitant rales or fine scratching rub may be heard; and decreased breath sounds.

Probably the most helpful diagnostic agent is the chest roentgenograph. It is not diagnostic but in combination with other findings gives the most satisfactory evidence of eosinophilic infiltration. Subsequently, roentgenograms, for comparative purposes, are important.

Laboratory Findings: Historically and characteristically, eosinophilia is the most important laboratory finding. Values from 10 to 60 per cent are most common, although values to 85 per cent have been reported. Peculiarly enough, the eosinophilia characteristically reaches its peak when the pulmonary infiltration has cleared. No parallelism between extent of eosinophilia and pulmonary infiltration can be made conclusively. The white blood count has been reported in Loeffler's syndrome from 8,000 to 15,000 Wbc/cm; higher values are not infrequent. The blood sedimentation rate is described as being slightly increased, from 8 to 15 mm. per hour. Values to 50 mm. per hour are also commonly reported. The examination of the sputum reveals the presence of eosinophils.

Causes of Eosinophilia:[19] 1) Allergic disorders; bronchial asthma, urticaria, angioneurotic edema, hay fever. 2) Skin diseases. 3) Parasitic infestations; especially parasites which invade the tissues. 4) Certain infections, as scarlet fever, chorea, erythema multiforme. 5) Certain diseases of the hemopoietic system. 6) Following irradiation. 7) Miscellaneous disorders as periarteritis nodosum, tumors of the ovary, or those involving serous surfaces or bone; certain poisons, Loeffler's syndrome. 8) Familial anomaly. 9) Topical eosinophilia. 10) Drugs as pilocarpine, camphor, mercury, ace-

tanilide, sodium salicylate, potassium iodide, phosphorus, arsenic, benzene and digitalis.

Diagnosis and Differential Diagnosis

As has been previously stated, factors that are pathognomonic of Loeffler's syndrome are not rigidly constant but the consensus of opinion includes the following factors necessary to make a diagnosis of Loeffler's syndrome as compiled by Freund and Samuelson:[20] 1) Signs of pulmonary disease by auscultation and percussion. 2) Changes in the lungs shown by roentgenograms. 3) Transience of pulmonary signs. 4) Increase in the eosinophiles of the blood. 5) Eosinophiles in the sputum.

In addition, these may be added: 1) Allergic history prior to the onset of symptoms. 2) Ordinary benign clinical course.

In considering differential diagnosis, such conditions as pulmonary tuberculosis, carcinoma, embolism with infarction, pneumonia, bronchial asthma with selective atelectasis, erythema nodusum, virus respiratory infections, and tropical eosinophilia have to be excluded. Differential diagnosis of these infiltrations by roentgenograms alone is sometimes extremely difficult. A good history particularly concerning allergies as asthma, hay fever, urticaria, or other hyperergic states is sometimes extremely helpful.

Differentiation of Loeffler's syndrome from pulmonary tuberculosis fortunately is ordinarily not difficult, due to the fact that serial x-rays of Loeffler's syndrome usually shows resolution within a matter of days. Presence of eosinophilia and persistently negative sputum likewise aids in the differentiation. In pneumonic processes the problem may be more difficult. The homogeneous, dense, lobar type of infiltration may suggest specific pneumonia. In virus pneumonia or the so-called atypical pneumonias, the pulmonary infiltrations may be as varied as that of Loeffler's syndrome. Symptoms likewise may be minimal but a lack of homogeneity of the shadow in atypical pneumonia may aid in the differentiation. The presence of eosinophiles in the peripheral blood is again significant.

Embolism with infarction usually presents some nonpulmonary findings as phlebitis with more persistent pulmonary infiltration, and usually more profound symptoms than Loeffler's syndrome.

Bronchogenic carcinoma may simulate the bizarre x-ray appearance of Loeffler's syndrome. A persistent x-ray shadow always suggests carcinoma. Bronchial asthma and erythema nodosum are differentiated in most cases with a complete history and the variations in roentgenograms.

Tropical eosinophilia[21] is an endemic disease, apparently widespread in the coastal regions of Southern India, characterized by

chronic paroxysmal cough, asthmatic breathing, weakness, listlessness, loss of weight, and marked leukocytosis: 20,000 to 60,000 white blood cells with eosinophilia of 50 to 80 per cent. Onset and physical signs are ordinarily benign while roentgenograms show a fine, diffuse mottling with irregular, ill-defined, pea-size areas of increased density scattered thickly throughout the lung fields. This condition responds spectacularly to neoarsphenamine.

Roentgenography: Loeffler describes the x-ray findings as one or more shadows of variable structure and size. They may be homogeneous or mottled in appearance, more or less circumscribed, unilateral or may be bilateral. Emphasis is placed on the transiency of the lesions. Originally the most common area involved was the subclavicular region of the right lung though more recently the lower lung fields. Duration of infiltration varies tremendously, although three to 10 days seems to be the average. Cases have been reported as persisting 32 months.[14] Occasionally, the pleura may be involved resulting in effusion. Infiltration may come in sporadic cycles, resolution may be taking place in one area while new infiltrations are appearing elsewhere.

Gottdiener classified five types: 1) Extensive, irregular shadows of varying density and homogeneity. 2) Nodular shadows. 3) Multiple cystic shadows. 4) Dense homogeneous shadows of lobar distribution. 5) Small infiltration resembling secondary tuberculous infiltrates.

We would suggest that healing or resolution of these infiltrates when complete is represented by a fine, strand-like shadow simulating a scar. Hennell and Sussman[23] state that a fine, oblique, plate-like shadow, which may be bilateral, is characteristic of these healed infiltrations and should suggest the correct diagnosis.

Prognosis: In the majority of cases, the prognosis is excellent in from one to three weeks. A few deaths have been reported[11,16,23] and other cases of death with concurrent Loeffler's syndrome could not be ascribed to the latter disease.

Complications: Pleural effusion with possible empyema; right ventricular strain due to increased resistance in pulmonary circulation being reversible as the exudate absorbs. Asthma and panarteritis have also been reported as complications of Loeffler's syndrome.

Treatment: Conservative treatment of bed rest and symptomatic treatment has controlled the majority of cases, though such agents as aminophyllin,[16,25] adrenalin,[18,24] roentgenotherapy,[26] have been used with reported success. Associated parasitic infestation and bacterial infections should be treated specifically. Arsenicals are perhaps of the greatest value.

Case Report

This man (G.S., No. 9924-47) a clerical worker of 59 years was admitted to Grant Hospital, Columbus, Ohio, with probable diagnosis of cancer of the right upper lobe on December 27, 1947, when he was first seen by the senior author (M.G.B.).

The chief complaints were cough since 1945, moderately severe at times, slight expectoration, slight wheeze in right chest, occasional shortness of breath, weakness, loss of weight, 25 pounds in six months, and loss of appetite.

Present Illness: The patient stated that he had the "flu" in 1943. Prior to that he had mild hay-fever. X-ray inspection of the chest in 1943, 1944 and 1945 were reported negative. In 1945 he lost his appetite, became nervous and quit work. His cervical lymph nodes were enlarged but he recovered within three months and was well until August 1947, when he began to lose weight and "go down hill." He developed cough, slight expectoration and wheezing. These symptoms persisted. He was advised to go to Florida for recovery. While there, following inspection of his chest by Dr. Frank L. Price, he was advised to return home because of probable carcinoma of the lung.

There was no history of tuberculosis or cancer in his family. In 1945 he was told he had trichinosis, at which time he probably had an eosinophilia. Since August 1947, he had lost weight, etc., until admission to Grant Hospital. Prior to admission he had received large amounts of penicillin (given every three hours for sixteen days) also sulfadiazine in the usual dosage.

On examination he weighed 112 pounds, was five feet seven inches tall.

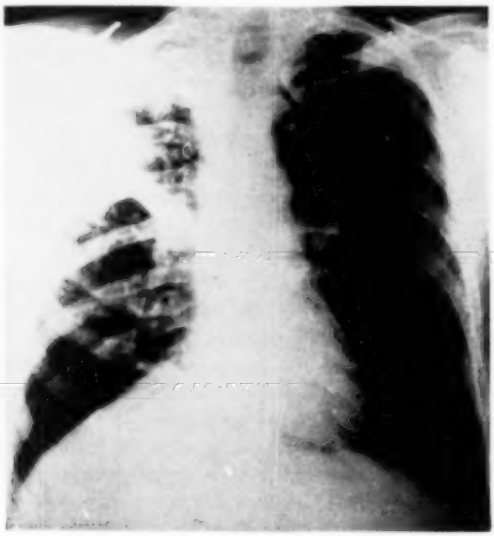


FIGURE 1

His pulse was 93 per minute, blood pressure 122 80 and temperature 99.2 degrees F. An occasional rhonchus was heard over the right upper lobe anteriorly and in the axilla. Bronchoscopic examination revealed no abnormality except a moderate amount of secretion, some of which was aspirated for bacteriological and cellular studies. X-ray films taken on December 30, 1947, and compared with those taken by Dr. Price in Florida showed slight clearing of the process in the right upper lobe. Our impression was that this probably represented an inflammatory process. Large amounts of penicillin and sulfadiazine, plus mapharsen were administered.

He reacted to tuberculin but acid fast organisms were not found on bronchoscopic aspirations. Urinalysis revealed 40 mgm. albumin. The sedimentation rate on December 29, 1947, was 28 mm. per hour. The sputum and bronchoscopic aspirations revealed monilia albicans on culture. The sputum contained eosinophils. Cells were also found which "were very suggestive of cancer cells." (Papanicolaou technic). On December 29, 1947, the red blood count was 4,640,000, hemoblobin 11.7, white blood count 12,100 with 43 per cent eosinophils.

X-ray inspection on January 4, 1948, revealed no evidence of clearing of the lesion and his condition remained unchanged clinically. It was felt that with a six months history of progressive disease, a persistent x-ray shadow, suspicious carcinoma cells in the bronchoscopic material, exploratory thoracotomy was justified, although we had not explained the persistent eosinophilia. Various other conditions such as trichinosis, Loeffler's syndrome, etc., were considered.

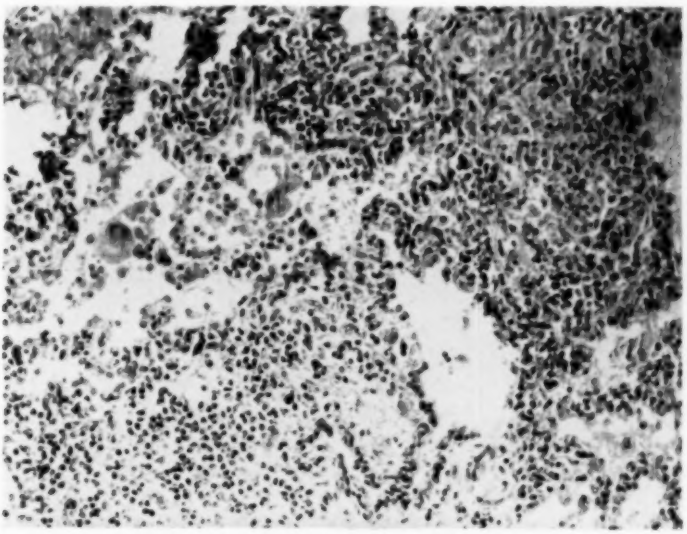


FIGURE 2: Granuloma of Loeffler's Syndrome showing eosinophiles, pale epithelioid cells, multinucleate giant cells, and partial destruction of bronchiolor wall. Magnification125.

Operative Report

On January 6, 1948, under endotracheal cyclopropane and ether anesthesia a right posterolateral thoracotomy incision was made. The sixth rib was removed in its entirety, followed by a portion of the seventh. The lung was found to be free in the pleural cavity with about 150 cc. of straw colored fluid present. The surface of the lung presented a tumefaction compatible with carcinoma, extending across the fissure line into the lower lobe and possibly involving the middle lobe. There was no procedure feasible with the exception of pneumonectomy. The lung was found to be fairly free on the mediastinal surface. The inferior pulmonary vein was doubly ligated with transfixion sutures and the vein divided. The superior pulmonary vein was isolated, ligated and divided. This exposed the right pulmonary artery which was freed, triply ligated, transfixed and severed. An accessary inferior pulmonary vein was discovered and doubly ligated and divided. The mediastinal contained numerous lymph nodes, even into the subcorinal area. The lung was severed and a second stump removal was exceedingly high, near the bifuraction. The stump was closed with individual silk through and through sutures, followed by removal of all of the lymph nodes in the mediastinum. These were sent to the laboratory for section. The mediastinal pleura was then drawn across the hilar area completely burying the stump in a satisfactory manner. All bleeding was controlled. The pleural cavity was irrigated with warm saline and 100,000 units of penicillin was introduced. The chest wall was closed in layers, individual silk sutures being used throughout with the exception of No. 1 plain catgut subcuticular suture. A silver foil dressing was applied. Continuous citrated blood, approximately 1250 cc. was ad-

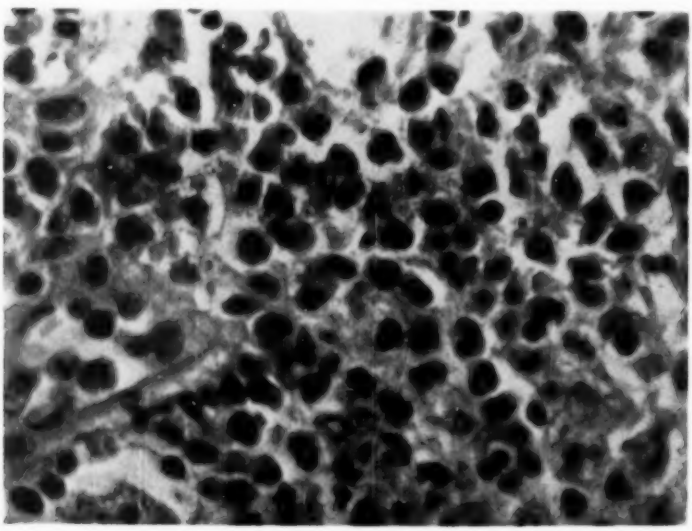


FIGURE 3: Eosinophilic infiltrate—high power of area enclosed in square on Figure 2. Magnification 400.

ministered during the procedure. Post-operative bronchoscopy revealing no bleeding of the stump and no accumulation of secretion in the left lung. The tissue was sent to the laboratory for examination. Due to the fact that this patient gave a history of trichiniasis a few sections of muscle tissue were taken from the latissimus dorsi muscle and sent to the laboratory for pathological study.

The patient's post-operative course was uneventful. He remained afebrile throughout, lost his cough and expectoration and almost immediately began to feel better. Ambulation was employed on the third day and thereafter. Penicillin, 50,000 units was introduced into the pleural cavity daily. He was discharged in good condition on January 24, 1948.

Pathological Report

Gross examination: Specimen consists of a right lung weighing 570 grams. It is hypocrepitant. The lateral surface is dried. The medial surface is mottled gray to yellow. The pleura is considerably thickened at the apex and over the upper half of the posterior border. The bronchi are cut off flush with the lung and on dissection are filled with bloody mucous. The bronchus to the upper lobe is surrounded by a firm yellow tissue poorly demarcated from the surrounding lung which reaches a thickness of 7 mms. This reaches the medial surface 6 cms. from the posterior border. The remainder of the upper lobe shows atelectasis and some thickening of the bronchi, which are somewhat dilated into the finer radicals. The anterior border of the upper lobe is quite solid and on section is deeply congested. The anterior border of the lower lobe is meaty and on cut section is deeply congested. The bronchi of the lower lobe do not show the congestion seen in the upper lobe. There is a small area beneath the capsule near the posterior border of the lower lobe which is firm and yellowish white in color. Separately is the main stem of bronchus and its earlier branches with surrounding lymph nodes. There is no gross evidence of tumor in this tissue. The mucous membranes show hyperemia and are covered with thick mucous. Also present are some gray-black irregular fragments of tissue presenting hilar lymph nodes varying from 1 to 3 cms. in diameter. The tissue is quite dried. The largest one contains a calcified nodule 1 cm. in diameter. The remainder are anthracotic without gross evidence of tumor metastasis. Also present are two pieces of skeletal muscle 2 and 2.8 cms. in diameter. They present no gross anatomical pathology.

Microscopic examination: Compatible with Loeffler's syndrome. The microscopic features are fibrosis with massive infiltration by eosinophiles, a pari-arteritis and arteriolitis with eosinophilia, granulomatous areas, endothelial cell proliferation with giant cells, and mononuclear phagocytes. There is no evidence of trichinosis.

Subsequent studies reveal: No increase of disease in the left lung on x-ray inspections with the exception of the usual changes expected on the operated side. On January 13, 1948, the red blood count was 4,610,000, white blood cells 11,750 with 12 per cent eosinophils. On January 24, 1948, there were 10,250 white blood cells with 12 per cent eosinophils. On March 21, 1948, there were 9,000 white blood cells with 3 per cent eosinophils.

Discussion

A case is presented which has more typically the course of bronchogenic carcinoma than eosinophilic infiltration, although the

latter was considered as a clinical probability. The exploratory thoracotomy resulting in pneumonectomy was done proving the diagnosis of eosinophilic disease which is commonly termed Loeffler's syndrome. It has been gratifying to the authors that a locally persistent eosinophilic granuloma has, at the end of 14 months, apparently responded satisfactorily to surgical extirpation.

SUMMARY

A case of Loeffler's syndrome is presented which was treated by complete pneumonectomy with favorable clinical response. As far as can be determined this is the first surgically treated case reported. This case conforms with all the diagnostic criteria in a limited degree and the diagnosis is confirmed by gross and microscopic pathological evidence.

RESUMEN

Se presenta un caso de síndrome de Loeffler que fué tratado por neumonectomía total con favorable resultado. Hasta donde puede saberse parece que este es el primer caso relatado en que se haya usado el tratamiento quirúrgico. El diagnóstico de este caso está acorde con el criterio clínico escasamente y el diagnóstico se confirmo por la evidencia macro y microscópica.

REFERENCES

1 Loffler, W.: "Zur. Differential—Diagnose der Lungen—Infiltrierungen," *Beitr. z. Klin. d. Tuberk.*, 79:368, 1932.

2 Hoff, A. and Hicks, H. M.: "Transient Pulmonary Infiltrations: Case with Eosinophilia (Loeffler's Syndrome) Associated with Amaebiasis," *Am. Rev. Tuberc.*, 45:194, 1942.

3 Slowery, J. F.: "A Case of Transient Successive Pulmonary Infiltration (Loeffler's Syndrome) Associated with Trichiniosis," *Ann. Int. Med.*, 21:130, 1944.

4 Elsom, K. A. and Ingelfinger, F. J.: "Eosinophilia and Pneumonitis in Chronic Brucellosis," *Ann. Int. Med.*, 16:995, 1942.

5 Muller, R. W.: "Transient Pulmonary Infiltration with Esoinophilia. Due to Ascarides in Larval Stage," *Beitz. z. Klin. d. Tuberk.*, 92:254, 1938.

6 Perlingiero, J. G. and Gyorgy, P.: "Chronic Eosinophilia," *Am. J. Dis. Child.*, 73:34, 1947.

7 Von Meyenburg, J.: "Eosinophilic Pulmonary Infiltration: Pathologic Anatomy and Pathogenesis," *Schweizerische Medizinische Wochenschrift*, 72:809, 1942.

8 Scherlis, S.: "Loffler's Syndrome," *M. I. Surg.*, 96:349, 1945.

9 Alpher, I. M.: "Loeffler's Syndrome," *J. Allergy*, 18:39, 1947.

10 Engel, D.: "Uber eine Eigenartige Anaphylaktische Erkrantung der Lunge," *Beitr. z. Klin. d. Tuberk.*, 87:239, 1936.

11 Harkavy, J.: "Vascular Allergy," *Anch. Int. Med.*, 67:709, 1941.

12 Alpers, I. M.: "Loffler's Syndrome," *J. Allergy*, 18:39, 1947.

13 Braeuning, E.: "Partielles Asthma," *Ztschr. F. Tuberk.*, 73:174, 1935.

14 Serra, L.: "Loffler's Syndrome," *Bull. Sch. Med. V. Mary.*, 30:11, 1945.

15 Hansen-Pruss, O. C. and Goodman, E. G.: "Allergic Pulmonary Consolidations," *Ann. Allergy*, 2:85, 1944.

16 Bayley, E. C., Lindbert, D. O. N. and Baggenstuss, A. H.: "Loffler's Syndrome," *Arch. Path.*, 40:376, 1945.

17 Saslaw, M. S. and Bowman, J. A.: "Loffler's Syndrome," *J. Florida M. A.*, 32:373, 1946.

18 Karan, A. A. and Singer, E.: "Transitory Pulmonary Infiltrations Mistaken for Tuberculosis," *Ann. Int. Med.*, 17:106, 1942.

19 Wintrobe: "Clinical Hematology," p. 172, *Lea and Febiger*, Philadelphia, 1946.

20 Freund, R. and Samuelson, S.: "Transitory Infiltration of the Lung with Eosinophilia (Loffler's Syndrome)," *Arch. of Int. Med.*, 66:1215, 1940.

21 Emerson, K. Jr.: "Tropical Eosinophilia," *U. S. Navy Med. Bull.*, 42: 118, 1944.

22 Gottdiener, E. E.: "The Diagnosis of Loffler's Syndrome," *New York State J. Med.*, 45:2179, 1945.

23 Hennell, H. and Sussman, J. L.: "The Roentgen Features of Eosinophilic Infiltrations in the Lungs," *Radiology*, 44:328, 1945.

24 Miller, H.: "Transitory Lung Infiltrations Accompanied by Eosinophilia," *New England J. Med.*, 232:7, 1945.

25 Ham, J. C. and Zimdahl, W. T.: "Loffler's Syndrome and Pulmonary Infiltration," *Ann. Int. Med.*, 29:488, 1948.

26 Ryan, J. M.: "Loffler's Syndrome," *Minn. Med.*, 27:734, 1944.

Pleural Effusions and Intrapleural Pressures of the Re-expansion Period in Pneumothorax

T. G. HEATON, M.B., F.C.C.P.
Toronto, Canada

This is a study of intrapleural pressures in cases of artificial pneumothorax, treated at Sunnybrook Hospital, Toronto, under the Department of Veterans' Affairs of Canada.

The study's purpose is to see what inferences can be drawn from these data with regard to the nature and prevention of pleural effusion in artificial pneumothorax particularly in the re-expansion period.

The pressures are recorded as read on the manometer of the Bethune pneumothorax apparatus. This manometer records "true pressures": that is, double the actual distance above or below zero in centimeters of water. Mean pressures are calculated from these readings.

In Table I are grouped cases of artificial pneumothorax who had no fluid visible on fluoroscopy of the chest either shortly before re-expansion was started, or during the re-expansion period, with or without pleural thickening.

Table II is comprised of data from pneumothorax cases who had some fluid seen on fluoroscopy either immediately before or during the re-expansion period and similarly followed to maximum expansion of the lung.

Both tables show intrapleural pressures on quiet breathing before refill, both immediately before and during the re-expansion period. The pressures recorded are the most highly negative pressures encountered during the three refills next prior to the re-expansion period, and during the re-expansion period, respectively.

Those selected for listing include all cases discontinued since December 10, 1948, and whose lungs had completely re-expanded before December 31, 1949. Re-expansion was managed by the gradual tapering off of refills except where otherwise noted in the tables.

Inspection of the mean pressures in both tables in the "during re-expansion" column indicates that there does not exist a critical mean negative pressure above which fluid forms in all cases, and below which fluid fails to form in all cases. It is inferred that the effusions of the re-expansion period are not ex-vacuo transudates in all cases. May they be ex-vacuo transudates in some of these cases?

The same columns indicate that in all cases in which the mean negative pressure is greater than −15, fluid has formed (six cases).

It is not possible to infer that effusions forming when negative pressures are greater than −15 are ex-vacuo transudates because: (a) It is possible that both the high negative pressures and the fluid have a common cause. (b) Clinical experience does not suggest that there are two kinds of clear effusion in the re-expansion period. One may however infer that negative mean pressures greater than −15 indicate the likelihood of fluid formation. Why?

If fluid develops ex-vacuo in the re-expansion period, then the negative pressure required may be expected to vary with the condition of the pleura. One would expect thin pleura to permit transudation more readily than thick pleura, i.e., at lower negative pressures. In Table III, group A consists of cases with no fluid, but with most highly negative pressures. If the ex-vacuo factor is important, one would expect the pleura in these cases to be thick, resisting transudation. Group B consists of cases with fluid and least highly negative pressures. One would expect the pleura

TABLE I

Cases Having No Fluid Immediately Before or During the Re-expansion Period

Name	Intrapleural Pressures before re-expansion period			Intrapleural Pressures during re-expansion period		
	Insp.	Expir.	Mean	Insp.	Expir.	Mean
Morris	−13	− 5	− 9.0	−13	− 7	−10.0
Ballantine	−12	− 8	−10.0	discontinued abruptly		
Ellis	−14	−12	−13.0	−17	−13	−15.0
Astle	− 9	− 5	− 7.0	discontinued abruptly		
Tyrrell	−12	− 7	− 9.5	− 9	− 4	− 6.5
McDowell	−10	− 5	− 7.0	−13	− 7	−10.0
McGibbon	− 9	− 4	− 6.5	− 9	− 4	− 6.5
St. John	−11	− 4	− 7.5	discontinued abruptly		
Bartlett	−12	− 8	−10.0	discontinued abruptly		
Yake	−11	− 6	− 8.5	discontinued abruptly		
Rush	− 9	− 3	− 6.0	−12	− 3	− 7.5
Wijatik	− 9	− 4	− 6.5	−14	−12	−13.0
Simpson	−15	− 8	−11.5	−11	− 6	− 8.5
Pearce	−12	− 5	− 8.5	−12	− 8	−10.0
			Average Mean −8.6			Average Mean −9.7

in these cases to be thin, readily permitting transudation. Table III shows the contrary to be the case.

The ex-vacuo factor, therefore, is not important in itself as a cause of the effusions of the re-expansion period. What then is important?

The difference between the average mean pressures before and during the re-expansion period of the "no fluid" cases in Table I is 9.7 minus 8.6, equals 1.1 cm. of water.

The difference between the average mean pressures before and during re-expansion period of Table II, the "fluid" cases, is 12.75 minus 9.40, equals 3.35 cm. of water. This is three times the difference in the first group.

Some preliminary discussion is necessary to support the infer-

TABLE II

Cases Having Fluid Immediately Before or During the Re-expansion Period

Name	Intrapleural Pressures before re-expansion period			Intrapleural Pressures during re-expansion period		
	Insp.	Expir.	Mean	Insp.	Expir.	Mean
Wallace	−10	− 4	− 7.0	−24	−11	−17.5
Fanuzzi, Rt.	−10	− 8	− 9.0	aspirated to re-expand		
Fanuzzi, Lt.	− 9	− 4	− 6.5	aspirated to re-expand		
Hall	−16	−11	−13.5	−12	− 6	− 9.0
Pypher	− 8	− 4	− 6.0	−10	− 5	− 7.5
Burridge	−10	− 6	− 8.0	−10	− 6	− 8.0
Stinson	−15	− 7	−11.0	−13	− 8	−10.5
Skinner	−13	− 9	−11.0	aspirated to re-expand		
Borek	−18	−11	−14.5	−20	−16	−18.0
Ellis (6676)	−11	− 5	− 8.0	−20	−13	−16.5
Waite	−14	− 7	−10.5	−17	−10	−13.5
Bedford	−12	− 6	− 9.0	−11	− 7	− 9.0
Hollins	−10	− 6	− 8.0	−20	−12	−16.0
Barrett	− 9	− 4	− 6.5	−19	−10	−14.5
Warne	−11	− 8	− 9.5	−19	−12	−15.5
St. Laurent	−17	− 6	−11.5	abruptly discontinued		
Leaman	−18	−11	−14.5	−20	−14	−17.0
Foley	− 8	− 6	− 7.0	abruptly discontinued		
Armstrong	−11	− 6	− 8.0	− 8	− 4	− 6.0
			Average Mean −9.4			Average Mean −12.75

ences which can be made. In pneumothorax cases high negative pressures develop when the lung resists expansion; that is fails to expand, or expands slowly, when refills are reduced in amount. Lungs fail to re-expand chiefly because of pleural thickening. When a lung is being re-expanded and the intrapleural mean pressures are seen to be more than 1.1 cm. of water greater than before the re-expansion period, it may be concluded that the lung is resisting re-expansion. The figure 1.1 is the difference between the average mean pressures before and after refill in the no fluid cases of Table I. It seems reasonable to infer that when this difference is greater than average the lung is resisting expansion. Hence that thickening of the visceral pleura is present. (In our series of "fluid" cases thickening of visceral pleura is therefore nearly always present). Thickening of visceral pleura prior to the start of re-expansion is therefore closely related to the occurrence of fluid in the re-expansion period. It is felt that this thickening of the visceral pleura is the factor which usually determines the occurrence of fluid during the re-expansion period, and, by inference, also often during the course of pneumothorax treatment.

How is this operative? One may attempt an answer. When the lung is in a state of partial or complete collapse its pleural surface area is smaller than when fully expanded. When the collapsed lung is allowed to re-expand, its pleural surface area must increase. When the pleura remains healthy, thin and elastic, this increase in pleural surface area is accomplished with no, or with minimum trauma. But when the visceral pleura is thickened and inelastic the increase in pleural surface area can be accomplished only by splitting of the thickened pleura. (Perhaps especially the fibrin layer superimposed upon the pleura). This trauma may well be the cause of pleural reaction and pleural effusion, presumably due to liberation of tubercle bacilli or their growth products into the pleural cavity.

The higher the intrapleural negative pressure, the greater the

TABLE III

GROUP A Name	X-Ray Appearance of Pleura	GROUP B Name	X-Ray Appearance of Pleura
Ellis (10884)	thick	Barrett	thick
Ballantine	thin	Fanuzzi, left	thick
Simpson	thin	Pypher	thick
Morris	thin	Foley	thick

trauma that occurs. This idea explains nicely the observation made above, that mean negative intrapleural pressures over −15 cm. of water are usually, if not always, followed by the development of pleural fluid. This pressure probably is that usually required to split and traumatize a considerably thickened visceral pleura.

Trauma is inevitable in the re-expansion of a lung with thickened visceral pleura. If this trauma is accomplished a little at a time the resulting harm to the patient is likely to be minimized. Therefore gradual expansion of the lung is to be preferred on theoretical grounds to abrupt cessation of refills, in all cases in which the lung resists expansion.

CONCLUSIONS

1) The effusions of the re-expansion period are not ex-vacuo transudates.

2) When the mean negative intrapleural pressure is greater than −15 cm. of water, the formation of fluid is most likely to occur, if fluid is not already present.

3) When the average mean intrapleural pressure during re-expansion is greater than that before re-expansion was started, by 1.1 cm. of water, then the lung is resisting expansion. Records should be sufficient to permit the observation of this pressure difference to be made.

4) The chief cause of pleural effusion in pneumothorax cases during re-expansion of the lung is trauma to thickened pleura incident to pneumothorax treatment.

5) Gradual re-expansion is usually to be preferred to abrupt cessation of refills. Exception may be made in cases in which the visceral pleura is thin and the lung has been observed to have a strong tendency to re-expand.

The writer expresses his thanks to Dr. J. F. Paterson, Chief Physician of the Chest Service of Sunnybrook Hospital for his interest and advice in connection with this study.

CONCLUSIONES

1) Los derranes del periodo dere-expansión no son transudados por ex-vacuo.

2) Cuando la presion intrapleural es por debajo de la negativa 15 cm. de agua, el derrame es muy probable que se forme, si no se ha formado ya.

3) Cuando el promedio de la presion intrapleural durante el periodo de re-expansión es mayor que la obtenida anteriormente;

por ejemplo, 1.1 cm. de agua, quiere decir que el pulmón está resistiendo la expansión. Deben tenerse suficiente datos de las presiones observadas y sus diferencias.

4) La causa principal del derrame pleural en el periodo de re-expansión del pulmón en casos con pneumotorax, es el traumatismo a la pleura espesada, provocado por el tratamiento del pneumotorax.

5) La re-expansión gradual es preferible a la brusca; excepto en los casos en los cuales la pleura visceral es muy fina y el pulmón tiende a expanderse.

Idiopathic Pulmonary Fibrosis; Its Occurrence in Identical Twin Sisters

J. WINTHROP PEABODY, M.D., F.C.C.P.,
J. WINTHROP PEABODY, JR., M.D.
Washington, D. C.

E. W. HAYES, M.D., F.C.C.P., E. W. HAYES, JR., M.D.
Monrovia, California

So-called idiopathic pulmonary fibrosis though of rare occurrence is assuredly one of the more striking diseases to be described in recent years. Seldom does the clinical picture fail to confuse the internist, while the microscopic pathology, at once so unusual and yet so distinctive, seems invariably to astonish the pathologist. Despite the remarkable nature of the disease the paucity of reported cases has relegated it to a place of relative obscurity. Although we must admit that the senior authors of this paper in practice confined largely to diseases of the chest have never until recently seen a case of this type, we feel certain nonetheless that so little attention has been accorded this condition, that it probably continues to baffle the occasional observer, and in the absence of an autopsy must often go completely unrecognized. With that in mind we shall attempt to clarify the meager existing literature and present a case report, the most remarkable feature of which is the occurrence of a clinically indistinguishable condition in the patient's twin sister.

In the vast majority of cases pulmonary fibrosis is of obvious origin, arising as a specific component of various disease entities. Among the infectious causes, tuberculosis, bronchiectasis and chronic Friedlander's pneumonia are the most prominent. Bronchial asthma either by the allergic nature of the disease or by impeding the resolution of pneumonic processes[12] may be associated with a considerable degree of fibrosis. The pneumoconioses and radiation pneumonitis[20] closely resemble the idiopathic variety by reason of the diffuse pattern of involvement, while beryllium poisoning,[7] chronic passive congestion,[14] xanthomatosis of the Hand-Shuller-Christian type,[2,6] cystic disease of the pancreas,[1] and the mycotic pulmonary diseases are associated with varying degrees of fibrotic changes in the lungs. Scleroderma,[13] Raynaud's disease,[11] and periarteritis nodosa have on occasion been the source of a diffuse collagenous hyperplasia in the interstitial tissue of the lung not unlike that of the idiopathic type, except that clear-cut vascular changes are present and have actually caused rather than

accompanied the pulmonary fibrosis. Into one or another of these categories fall practically all cases of pulmonary fibrosis, but over and beyond these there is a type peculiar in its extent and to which no cause can be ascribed. This constitutes the idiopathic variety.

Idiopathic pulmonary fibrosis may be defined as an irregularly progressive pulmonary disease of unknown etiology characterized clinically by dyspnea, chronic cough and cyanosis in association with minimal lung findings, and pathologically by a startling degree of wide-spread hyperplasia of the interstitial pulmonary connective tissue. This collagenous hyperplasia may terminate in one of two ways. First, by the destruction of elasticity of the lung and obliteration of alveoli respiratory ventilation is diminished and pulmonary insufficiency results. On the other hand this insufficiency in conjunction with the decrease in the pulmonary vascular bed which accompanies fibrosis may lead to pulmonary hypertension and eventually to cor pulmonale. In either event death ensues, whether by suffocation due to pulmonary insufficiency, or by drowning in the pulmonary edema of right heart failure. There is no significant predilection for either exitus in the cases on record. It is our impression, however, that the more acute the case, the greater the tendency for cor pulmonale to exist. This is borne out by the cases so far reported, including our own which was chronic and free from right cardiac dilatation. To draw any conclusion from so small a series would of course be absurd, but it would stand to reason that a superimposed cor pulmonale should certainly lend momentum to an already downhill course.

Hamman and Rich[4] in the original description of this entity reported three cases of what they termed acute, fulminating, diffuse, interstitial fibrosis of the lungs. In 1944 they published a more detailed discussion and included another case report.[5] Since then two additional cases have been described, one by Eder, Hawn and Thorn,[3] and the other by Potter and Gerber.[15] These six cases comprise all reported instances of this disease and with but slight variations conform with great similarity to the original.

However, one revision of the original work would seem indicated, and that is deemphasis of the idea that this is an acute disease. The cases of Hamman and Rich were, it is true, of brief duration, lasting in one instance but 31 days from onset of symptoms to death. Potter's case on the other hand survived nine months after the initial complaints. Our case similarly pursued a contrasting course marked by exacerbations and remissions over a three and one half year period, but in the terminal phase the course was truly fulminating and comparable to those heretofore described. We wonder if the disease is not of its essence a prolonged, chronic affair which remains completely subclinical until the respiratory

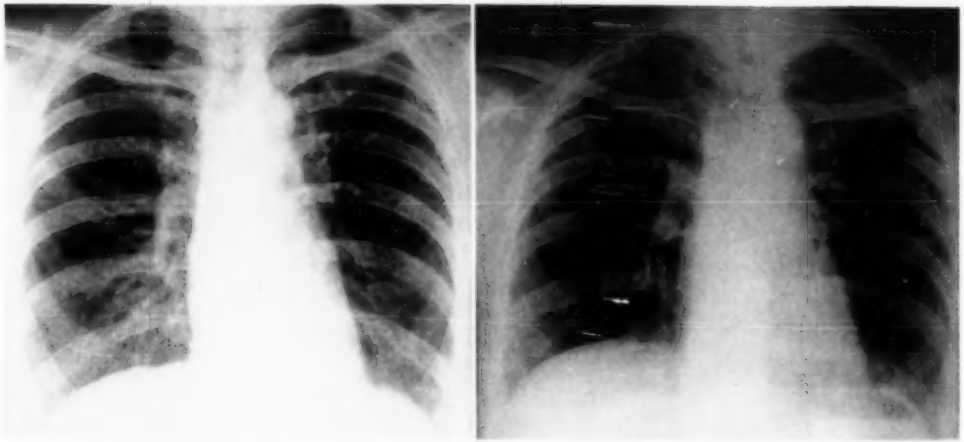


FIGURE 1 FIGURE 2

Fig. 1: From an x-ray film taken when we first saw Twin A in June, 1945, reveals bilateral apical densities of a somewhat granular appearance extending down to the second interspace.—*Fig. 2:* From film taken in November, 1946, when clinically the patient was doing rather well. The apical opacities have increased in density and there is extension of the granular process throughout the right lung and upper third of the left.

reserve is finally depleted, at which time symptoms appear and the fulminating portion of the disease runs its course. As Mallory[12] has pointed out, the reserve factor in progressive pulmonary fibrosis is so great that the lesions must be far advanced or even terminal before symptoms referable to pulmonary insufficiency occur. We feel that this latent but active period of the disease was a probable prelude in every case in the literature and that the case which we are about to cite was unique in that the latent period reached a level of clinically manifest disease due to episodes of exposure to various irritating agents.

Case 1: The first patient whom we shall call Twin A was first seen by one of us (J.W.P.) in June, 1945. She was 44 years old and her past medical history, although marked by fairly frequent illness, was not of particular significance. Her present illness and complicated course is herewith presented in summary.

In November, 1944, Twin A developed a persistent cough and sensation of tightness in the chest which she attributed to the fumes of an ever-smoking coal stove located in the same room in which she worked. In May of 1945, she had a severe cold and laryngitis associated with moderate dyspnea and aggravation of the cough. Soon afterward, because of suspicious lesions detected in mass x-ray survey, she was advised to consult a chest physician. Although physical examination of the chest was negative, her symptoms were suggestive of tuberculosis, as was the chest x-ray film (Fig. 1).

Symptoms of cough, hemoptysis and exertional dyspnea improved in the summer of 1945, during a stay in the mountains; were aggravated during the following winter which was spent in a damp location by the

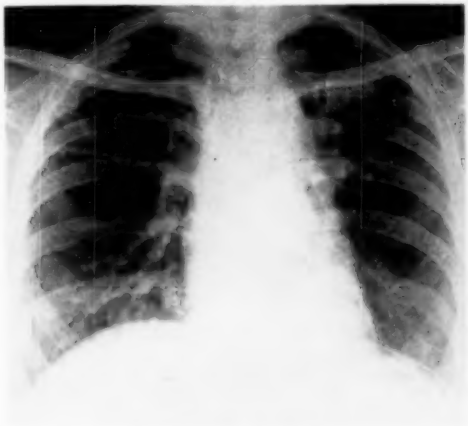


FIGURE 3: From a roentgenogram taken in March, 1947, showing distinct evidence of progression. There is a generalized granular appearance throughout both lungs with some thickening of the interlobar fissure between the upper and middle lobes on the right.

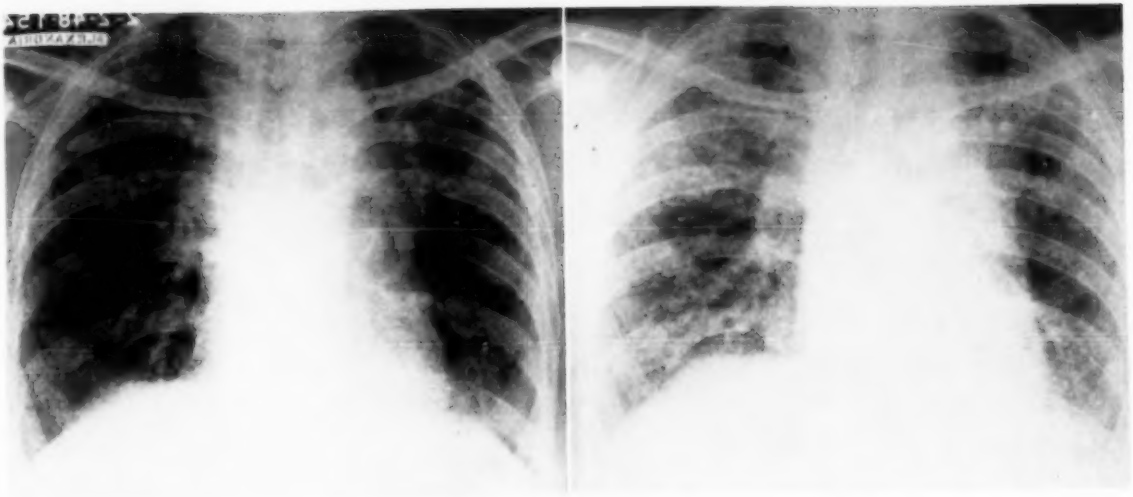


FIGURE 4

FIGURE 5

Fig. 4: From a roentgenogram taken in February, 1948, revealing an increase in the general fibrotic condition with an extension of the hilar shadows especially on the left.—*Fig. 5:* From an x-ray taken two weeks after Figure 4. Even in the two week interval between films there is evidence of progression. Widening of the upper third of the mediastinum is now present and the diaphragm is elevated. At this time tuberculosis was definitely excluded and a chronic interstitial type of pulmonary fibrosis was regarded as the most reasonable diagnosis. Death occurred about three months later.

river and again improved after a summer in the country in 1946. From that time until January, 1948, the patient enjoyed reasonably good health, although x-ray inspections demonstrated obvious progression of the process (Figs. 2 and 3). Actually she was never symptom-free and on two occasions in late 1947 had greatly intensified cough and dyspnea when a visiting relative kept the apartment filled with cigar smoke.

In January, 1948, the patient's symptoms became much worse. As in the past they included coughing spells which were now severe, prolonged and frequent, and dyspnea now of marked degree and unrelieved by rest. She had a constant, ineffectual desire to raise sputum which was scant, frothy and sometimes streaked with blood. Within a month she had developed cyanosis and was in great respiratory distress. X-ray films at this time taken only two weeks apart reveal distinct evidence of progression (Figs. 4 and 5), but examination of the chest was quite out of accord with the severity of symptoms which now paralleled the x-ray findings. Of a multitude of laboratory tests the only positive finding was moderate compensatory polycythemia. Repeated studies for acid-fast bacilli were always negative throughout her illness.

With the onset of cyanosis the course went rapidly down-hill. She complained of precordial pain and almost continuous sore throat. The coughing spells, dyspnea and cyanosis grew worse. Continuous oxygen was required. Sulfonamides, penicillin, streptomycin, and anti-histamines were given abundantly but without benefit. The white count remained within normal limits. Fever was absent until the last month and never exceeded 100 degrees F., but the pulse showed a compensatory tachycardia remaining close to 140, while respirations were panting in character and ranged from 40 to 48 per minute. On June 7, 1948, three years and seven months after the first symptoms, Twin A expired of what can best be described as chronic suffocation. She had no evidence of right heart failure prior to death.

Autopsy

Gross: This was the body of a well-developed, well-nourished, 46 year old white female showing marked cyanosis of the face, neck, mucous membranes, and nail beds. The relevant findings were confined to the chest. Grossly the lungs were not impressive. The right lung weighed 400 Gms., and the left 380 Gms., both being firm and characterized by a diffuse fibrous texture. However, on section no crepitation was apparent and both lungs presented a red, fleshy appearance. There was no free fluid in either pleural cavity, and no pleural adhesions were noted. The diaphragm was markedly elevated. The bronchi, major vessels, and tracheobronchial lymph nodes all appeared normal.

Microscopic: Sections from all lobes of the lungs showed a similar picture. On all sections there was a severe distortion of the normal lung parenchyma. The visceral pleura was markedly thickened and showed areas of diffuse scarring. Nearly all of the alveoli were completely obliterated, having been replaced by dense, hyalinized connective tissue, while in other areas there was a fibroblastic reaction. The remaining alveoli were lined by cuboidal cells. The bronchi showed a diffuse lymphocytic infiltration with considerable thickening of their walls. The bronchioles were dilated and filled with an inflammatory exudate containing polymorphonuclear leukocytes. Most of the bronchioles were lined by hyperplastic columnar epithelium and often showed a striking metaplasia to

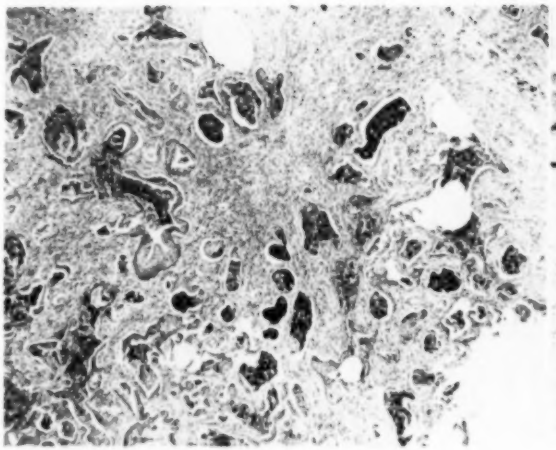


FIGURE 6

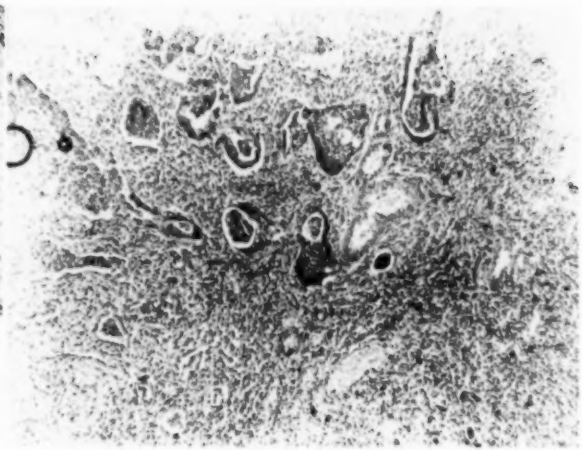


FIGURE 7

Fig. 6: Section of lung showing diffuse fibrosis, infiltration of chronic inflammatory cells and squamous metaplasia of bronchiolar epithelium. X 30.—*Fig. 7:* Section of lung showing decreased number of alveolae, fibrosis and squamous metaplasia. X 50.

squamous epithelium. The intervening stroma is fibrotic and diffusely infiltrated by chronic inflammatory cells consisting of lymphocytes, macrophages, and plasma cells. Some of the lymphoid tissue showed follicle formation. A few of the alveoli were filled with hemosiderin and fat-filled macrophages. The vessels were marked by intimal thickening. The lymphatics were markedly dilated and filled with lymphocytes. Congestion was present throughout, but is regarded as terminal in character.

Examination of the heart was essentially negative.

Comment

There are many points worthy of discussion. To one handling this case perhaps the most striking feature was the absence of significant physical findings in the face of radiological evidence of far-advanced pulmonary disease. Potter in his excellent analysis[15] calls attention to such a disparity which he attributed to the fact that the pathology is primarily interstitial in nature and therefore associated, as in primary atypical pneumonia, with a minimum of clinical findings.

It would perhaps be well to mention the usefulness of fluoroscopy as an adjunct to roentgenography in the diagnosis of pulmonary fibrosis. In this regard Robbins[17] stresses four points; one, the tendency toward fixation of the diaphragm in an elevated position; two, the conversion of the expiratory motion of the diaphragm from one that is only minutely slower than the inspiratory to one that is markedly slower; three, the paradoxical widening of the mediastinum on inspiration rather than the usual narrowing; and finally, the widening of the trachea on inspiration. The presence of one or more of these features may be diagnostic in a particular

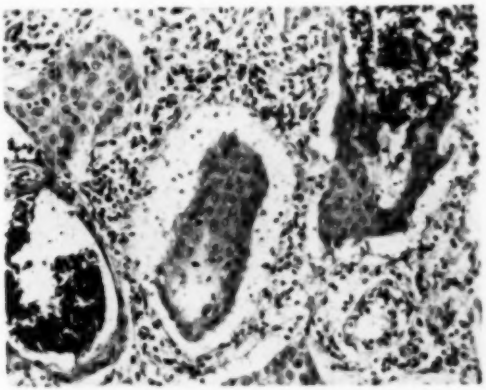


FIGURE 8: Section of lung showing marked squamous metaplasia. X 200.

case. It is of course of no value in differentiating pulmonary fibrosis of different etiologies.

This brings us to the point of just what is the etiology of this peculiar type of diffuse pulmonary fibrosis. No satisfactory explanation has so far been demonstrated as the label "idiopathic" indicates. Various causes have been suggested from time to time. Pulmonary fibrosis has been described by Linenthal and Talkov,[11] in conjunction with Raynaud's disease. These authors regard it as entirely possible that an occasional obscure case of pulmonary fibrosis may be Raynaud's disease preferentially localized to the lungs rather than the digits. The absence of the typical vascular changes of Raynaud's disease is strongly opposed to this possibility. The incrimination of scleroderma acting by a similar mechanism as proposed by Murphy et al,[13] can be disposed of for the same reason.

Recently Mallory,[12] in reviewing 6,000 consecutive autopsies at the Massachusetts General Hospital found six cases of a peculiar type of pulmonary fibrosis in each of which he was able to demonstrate the tuberculoid lesions of Boeck's sarcoid. It is at once obvious that our case and those heretofore reported bear no resemblance to sarcoid. In this case despite a pointed search for non-caseating tubercles, the pathologist was unable to demonstrate any pathology remotely resembling that of sarcoid. Moreover, Hampton in discussing Mallory's paper makes the statement that never has he seen sarcoidosis lead to fibrosis of the lung. More accurately this might be stated that although various pathologists have demonstrated microscopic evidence of healing of sarcoid lesions by fibrosis, it is seldom sufficient to cause x-ray changes. Actually we regard tuberculoid formation as a completely non-specific entity occurring with many diseases of which Hodgkin's is a notable example. Rich[16] mentions leprosy, syphilis, typhoid fever, lymphogranuloma inguinale, brucellosis, tularemia, torulosis and schistosomiasis as other diseases in which typical epitheliod tubercles occur. Hartz and Van der Sar[18] have observed a tuberculoid stromal reaction in a retroperitoneal neurocytoma, while Hardy and Tabershaw[7] cite the occurrence of epitheliod cells in a case of beryllium poisoning. We have personally noted such a reaction in silicosis, lipoid pneumonia and certain foreign body responses, as for example, in abdominal adhesions in response to talc deposition and even in the reaction tissue at the site of a Frei test.

The question of an allergic factor cannot be so lightly dismissed. Hamman and Rich[5] describe the presence of eosinophilic infiltration of the stroma as one of the pathological peculiarities of the disease, a point compatible with an allergic manifestation. How-

ever, repeated sputa examination for eosinophiles were negative in the case of Twin A. We have no idea as to what underlying sensitivity, if any, might be responsible and regard our present knowledge as too inadequate to form an opinion either pro or con. However, we do disregard the possibility of indicting certain noxious fumes as inciting agents. We are of the opinion that these factors serve merely to raise subclinical symptoms to a level of clinical recognition.

In the light of so marked an inflammatory infiltration as this case exhibits, the pathologist would be hard put to accept any etiology other than infectious. The inability to culture out significant bacteria only serves the more strongly to implicate a virus, and the lack of leucocyte response in the blood is of course in keeping with this view. Moreover, the disease undoubtedly occurs in localized form from which the patient recovers. As Hamman and Rich[4] point out, an occasional autopsy will reveal as an incidental finding a localized patch of pulmonary fibrosis identical in every respect with what we see here. Occasionally too we have seen a resected lobe present the same picture. Such cases are usually signed out by the pathologist as chronic fibrosing pneumonitis. If we accept such instances as localized forms of the same entity, the possibility of a viral etiology in this disease gains additional plausibility.

Finally, the constitutional factor must be considered. This has been singularly stressed in the field of chronic pulmonary disease

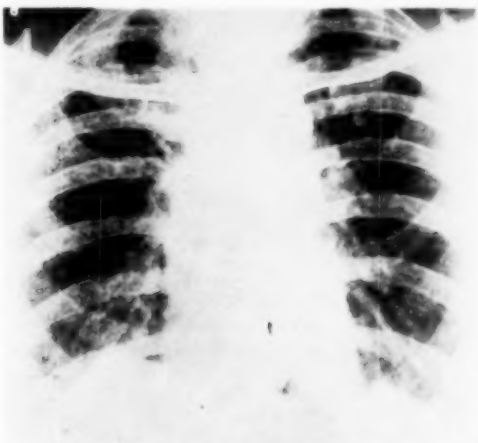


FIGURE 9: Our first x-ray film of Twin B taken in December, 1947, reveals a generalized fibrosis of both lungs.

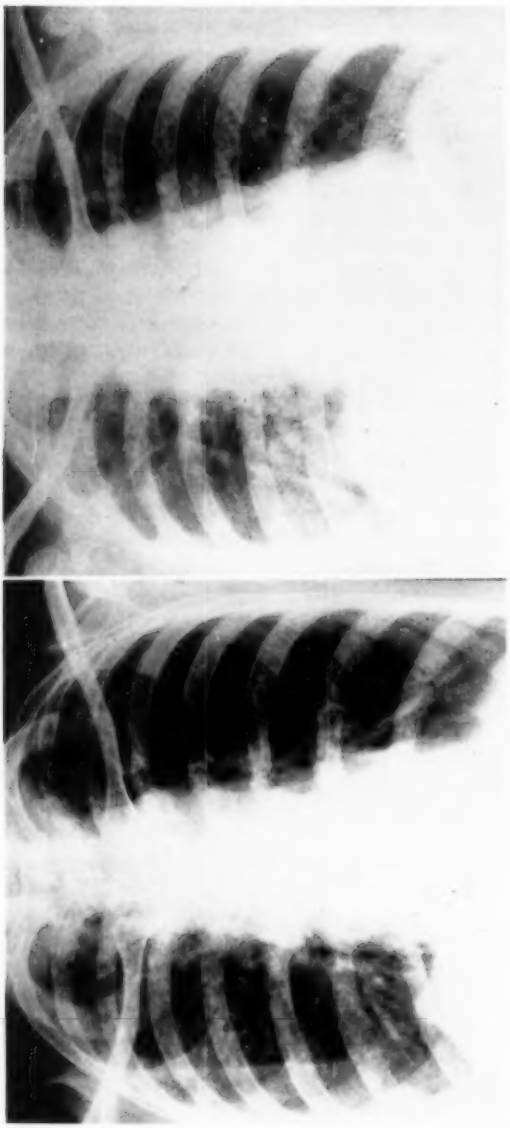


FIGURE 10

FIGURE 11

Fig. 10. From a roentgenogram in February, 1948, which shows a diffuse granular type of fibrosis throughout both lung fields more marked on the right.—*Fig. 11:* The most recent film taken in May, 1949, shows extension of the fibrotic involvement, a picture consistent with a diagnosis of idiopathic pulmonary fibrosis.

and to our minds seems significant in considering the case of the identical surviving twin of this case report.

Case 2: Except for influenza Twin B has essentially the same past history as the deceased. Sore throats, like those of her sister, constitute a chief but unexplained complaint. In 1943, she first noted the onset of exertional dyspnea, easy fatiguability and increased severity of her chronic sore throats. In February, 1946, 16 months after Twin A's first symptoms, she began to have bouts of extreme dyspnea. Over the intervening period the sore throats have become worse. The dyspnea has not changed in its severity, but is at present associated with wheezing, is more constant in occurrence and is greatly aggravated by paint and gasoline fumes.

Tuberculosis and bronchial asthma have been satisfactorily ruled out and there is no history suggestive of pneumoconiosis. Our clinical impression, perhaps presumptive, but substantiated by the x-ray findings (Figs. 9, 10 and 11) and symptomatology, is that Twin B is in a latent period similar to that which her sister experienced prior to the onset of the acute final phase.

The study of Kallman and Reisner[9] on inheritance and tuberculosis remains one of the finest demonstrations of the importance of the genetic factor in disease. These authors found that the chance of developing pulmonary tuberculosis by the age of 29 is 1.4 per cent of the general population, 7 per cent for husbands and wives of index cases, 25 per cent for siblings, 25 per cent for fraternal twins, but 87.3 per cent for the identical twin of an index case. This clearly indicates the influence of constitution on certain diseases. The genetic factor has been similarly stressed recently in a report on sarcoidosis in twins.[19] Idiopathic pulmonary fibrosis is so unusual that its occurrence in identical twins can hardly be attributed to coincidence. The fact that these twins led widely separated lives for at least 25 years prior to onset of the disease is another point suggesting some inherent constitutional tendency. If our assumption be correct, viz., that the surviving twin has idiopathic pulmonary fibrosis, then it would appear beyond question that, as with tuberculosis, there exists in certain individuals a strong constitutional tendency toward this disease.

It will be a matter of great interest to follow the course of Twin B. No known therapy is now available. Massive amounts of aerosol and parenteral penicillin failed to alter the course of Potter's case and ours as well. Should further studies confirm the efficacy of aureomycin against viruses other than that of primary atypical pneumonia[13] a course of the drug might prove worthwhile in the event of an acute exacerbation in Twin B. Taking a more optimistic view, it may be that the surviving twin, whose illnesses have always tended to be less severe than her sister's may enjoy a happier fate and that her disease will remain stationary.

SUMMARY

1) Idiopathic pulmonary fibrosis may be defined as an irregularly progressive pulmonary disease of unknown etiology characterized clinically by dyspnea, chronic cough and cyanosis in association with minimal lung findings, and pathologically by a startling degree of wide-spread hyperplasia of the interstitial pulmonary connective tissue.

2) The brief literature is reviewed and an additional case reported, the most remarkable feature of which is the occurrence of a clinically indistinguishable condition in the patient's identical twin sister.

3) Possible etiologic factors are discussed, the constitutional factor being stressed because of the genetic implications contained in this case report.

The authors wish to express their indebtedness to the following for their invaluable assistance in preparing this paper: William W. Ayres, Comdr., Medical Corps, U.S.N.; Dr. Lyman C. Boynton, Fairport, N. Y.; Dr. Ezra Bridge, Rochester, N. Y.

RESUMEN

1) Puede definirse la fibrosis pulmonar idiopática como una neumopatía de evolución irregular, de etiología desconocida, caracterizada clínicamente por disnea, tos crónica y cianosis, asociada con hallazgos pulmonares mínimos y, patológicamente, por un grado sorprendente de hiperplasia difusa del tejido conectivo intersticial pulmonar.

2) Se repasa la breve literatura y se informa sobre un caso adicional, el rasgo más extraordinario del cual es la ocurrencia de un estado clínico indistinguible en la hermana gemela idéntica.

3) Se discuten los posibles factores etiológicos y se hace hincapié sobre el factor constitucional debido a las inferencias de carácter genético incluídas en este informe.

REFERENCES

1 Attwood, C. T. and Sargent, W. H.: "Cystic Fibrosis of the Pancreas with Observations on the Roentgen Appearance of Associated Pulmonary Lesions," *Radiology*, 39:417, 1942.

2 Currens, J. H. and Popp, W. C.: "Xanthomatosis-Hand-Schuller Christian Type; Report of a Case with Pulmonary Fibrosis," *Am. J. Med. Sc.*, 205:780, 1943.

3 Eder, H., Hawn, C. V. and Thorn, G.: "Report of a Case of Acute Interstitial Fibrosis of the Lungs," *Bull. Johns Hopkins Hosp.*, 76:163, 1945.

4 Hamman, L. and Rich, A. R.: "Fulminating Diffuse Interstitial Fibrosis of the Lungs," *Tr. Am. Clin. and Climat. Assoc.*, 51:154, 1935.

5 Hamman, L. and Rich, A. R.: "Acute Diffuse Interstitial Fibrosis of the Lungs," *Bull. Johns Hopkins Hosp.*, 74:177, 1944.

6 Hampton, A. O.: "Hand-Schuller-Christian Syndrome with Diffuse Pulmonary Fibrosis," *New England J. Med.*, 226:392, 1942.

7 Hardy, H. L. and Tabershaw, I. R.: "Delayed Chemical Pneumonitis

Occurring in Workers Exposed to Beryllium Compounds," *J. Indust. Hyg. and Tox.*, 28:197, 1946.
8 Hartz, P. H. and Van der Sar, A.: "Tuberculoid Reaction in a Retroperitoneal Neurocytoma," *Am. J. Clin. Path.*, 15:473, 1945.
9 Kallman, F. J. and Reisner, D.: "Twin Studies on the Significance of Genetic Factors in Tuberculosis," *Am. Rev. Tuberc.*, 47:549, 1943.
10 King, D. S.: "Pulmonary Fibrosis, Clinical Aspects," *Radiology*, 51: 477, 1948.
11 Linenthal, H. and Talkov, R.: "Pulmonary Fibrosis in Raynaud's Disease," *New England J. Med.*, 224:682, 1941.
12 Mallory, T. B.: "Pathology of Pulmonary Fibrosis, Including Chronic Pulmonary Sarcoidosis," *Radiology*, 51:468, 1948.
13 Murphy, J. R., Krainin, P. and Gerson, M. T.: "Scleroderma with Pulmonary Fibrosis," *J.A.M.A.*, 116:499, 1941.
14 Parker, F. Jr. and Weiss, Soma: "The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis," *Am. J. Path.*, 12: 573, 1946.
15 Potter, B. P. and Gerber, I. E.: "Acute Diffuse Interstitial Fibrosis of the Lungs; Report of a Case," *Arch. Int. Med.*, 82:113, 1948.
16 Rich, Arnold R.: "The Pathogenes of Tuberculosis," *Charles C. Thomas*, Springfield, p. 722, 1944.
17 Robbins, L. L.: "Idiopathic Pulmonary Fibrosis; Roentgenologic Findings," *Radiology*, 51:459, 1948.
18 Schoenbach, E. B. and Bryer, M. S.: "Treatment of Primary Atypical Nonbacterial Pneumonia with Aureomycin," *J.A.M.A.*, 139:275, 1949.
19 Scherer, J. F. and Kelley, R. T.: "Sarcoidosis in Identical Twins," *New England J. Med.*, 240:328, 1949.
20 Widmann, B. P.: "Irradiation Pulmonary Fibrosis," *Am. J. Roentgen.*, 48:571, 1942.

Discussion

BENJAMIN L. BROCK, M.D., F.C.C.P.
Downey, Illinois

A review of the literature reveals that this most unusual disease first described by Hamman and Rich under the term "Acute Diffuse Interstitial Fibrosis of the Lungs," has been reported in only six cases previously. The comparative rarity of the disease has undoubtedly been responsible for the failure in the early recognition of the pathological process. The symptom complex of dyspnea and cyanosis characteristically comes on unusually early and progresses rapidly to fatality. Since the cause of the disease has not as yet been discovered, our efforts should be directed not only to the early diagnosis of the disease, but to the identification of the causative agent. Only in this way may we hope to prevent some of these cases at least from progressing to fatality.

Although purely speculative, the most logical suggestion is that the causative agent is a virus. Winternitz examined the original specimens submitted by Hamman and Rich and observed that the pathological changes in the lungs resembled those as seen in his animals in his studies on experimental influenzal pneumonia.

I have been unable to find to what extent laboratory research

has gone in an effort to determine the cause of acute diffuse fibrosis of the lungs. If the work of Winternitz has not been repeated, this naturally should be done with the use of material expectorated by a patient suspected of having the disease, or with material obtained from the lungs of an individual dying of the disease.

In 1936, Sabin and Olitsky reported a successful cultivation of poliomyelitis virus in test tube suspensions of human embryonic nerve tissue. Since growth could not be obtained from other human embryonic tissues, it was concluded that this virus is strictly neurotropic. It is possible that if we are dealing with a virus as a cause of acute diffuse fibrosis of the lungs, it may be specific for lung tissue or at least for tissues in the respiratory tract. The fact that the same disease has occurred in the lungs of identical twins is also suggestive of specificity.

Proliferation of the alveolar epithelium as reported in Potter's case and also in this case is interesting and suggests again that the causative agent may be similar to that which is responsible for the so-called alveolar cell carcinoma of the lung. This latter disease resembles closely the interesting adenomatous lung disease in South Africa sheep described by Cowdry, a disease known as jaagziekte and probably caused by a virus.

It is quite possible that different degrees of cellular activity, as indicated in the above conditions, may be the result of different degrees of stimulation or irritation whether this be from a virus infection or some other unknown agent.

In certain instances, the clinical syndrome of primary atypical pneumonia has appeared to respond dramatically to aureomycin. When a case of acute diffuse interstitial fibrosis of the lungs is suspected, aureomycin or other antibiotics such as chloromycetin should be administered. If the patient responds favorably to the action of these antibiotics, we may never know the true nature of the disease, but we may have saved a life. Should the patient succumb following such therapy and the disease is proved to be acute diffuse interstitial fibrosis of the lungs, the possible effects of the antibiotic on the pathological process may be studied. Even by such indirect methods, we may arrive at a possible solution of this interesting problem.

Pulmonary Hemorrhage: Its Control by the Use of Intravenous Pituitrin

HAROLD GUYON TRIMBLE, M.D., F.C.C.P. and
JAMES ROBERT WOOD, M.D.
Oakland, California

Pulmonary bleeding falls into three categories. The first is that of massive hemorrhage which is almost immediately fatal. This may be from the rupture of an aortic or other aneurysm into the bronchial tree or, more commonly, the rupture of a large pulmonary vessel, commonly a Rasmussen's aneurysm.[1,4,5] If the doctor were standing by the bedside, nothing could be done to control this type of fatal hemorrhage.

Secondly, there is the rarely persistent, never fatal, type of bleeding that consists of little more than blood streaking, may involve the raising of clots, comes frequently in the early morning hours, and presents no therapeutic problem as far as the bleeding itself is concerned. This type of bleeding is self limited though it may recur. Therapeutic measures are designed more to allay the fear and apprehension of the patient rather than toward the bleeding itself. The only caution that should be given here is that sedatives that markedly impair bronchial drainage are hazardous and should not be used. This applies particularly to relatively large doses of morphine and it's derivatives or similar synthetic compounds that may almost completely suppress the cough reflex.

There is a third type of hemorrhage intermediate between these. This type is brisk, not immediately fatal, but if allowed to continue may then produce other complications such as atelectasis and other interference with the bronchial drainage, or eventually, if continued, exsanguination. It is this type of hemorrhage which is the subject of our present discussion.

In this presentation we are not primarily interested in the disease that is responsible for the pulmonary hemorrhage, although the cause of any bleeding is of the utmost importance and must be ascertained in each patient. Suffice it to say that, in the order of frequency in our patients, these hemorrhages were due to various diseases such as tuberculosis, bronchiectasis, tumors, occasionally coccidioides, more rarely heart disease or a large number of other diseases which less frequently produce this symptom. It is also true that the mechanics of the pulmonary vascular tree are such that hemorrhage is usually controlled by simple measures. A program of strict bed rest with the patient lying on the side

from which the blood is coming, if known, very mild sedation of the cough reflex, an ice bag applied to the chest and reassurance that the bleeding itself is not likely to be serious, is enough to control a majority of such cases.

This paper is not concerned with those more easily controlled cases of pulmonary hemorrhage but rather with the control of hemorrhage in the occasional patient who continues to spit up large amounts of blood to such an extent that the loss in itself may become a life threatening matter.

Our attention was first drawn to the use of intravenous pituitary extract for this purpose by the late Max Pinner following his review of a recent book by the French physician, Edouard Rist.[7] The use of pituitrin intravenously as the best available agent to control pulmonary hemorrhage was first suggested in 1911 by the physiologist Carl J. Wiggers.[9,10] In a series of experiments with a number of different drugs, Wiggers concluded: "The drug that combines an ability to elevate the systemic arterial pressure and simultaneously to lower that in the pulmonary circuit, is the ideal physiological agent to employ. In the entire gamut of drugs investigated, pituitary extract is the only one that possesses this fortunate combination of actions." Rist, after reading Wigger's report, began to use pituitary extract intravenously to control severe hemoptysis in his patients. In 1913 he reported to the Medical Society of the Hospital of Paris, 12 cases with the almost immediate stopping of pulmonary hemorrhage which could not be controlled by other methods.[6] In his book published in 1943, he states: "Intravenous injection of pituitrin is so superior to the other treatments of hemoptysis that it is perhaps not very profitable to spend time on the other drugs used medically for this purpose." Rist remarked on the fact that the work done by Wiggers was not further followed in the United States. However, this is not correct, for the work of Wiggers was noted by physicians in this country, but unfortunately instead of using the drug intravenously as described in Wigger's paper, they began to use it intramuscularly. Used in this manner the haemostatic action of the drug is not sufficient to control pulmonary bleeding from a pulmonary artery or vein. It must be used intravenously to accomplish this purpose.[2,3,8]

Since we first began to use intravenous pituitrin to control pulmonary bleeding we have supervised it's administration on 46 occasions in a series of 32 patients in our own private practice, on the wards of the Alameda County Hospital and elsewhere. It's use for this purpose has been generally adopted and has become common practice among the chest men of our area. The control of the bleeding is quite prompt; it is almost as though one had

applied forceps directly to the bleeding vessel. Following the injection, the patient does continue to raise clots of blood and small amounts of blood-streaked sputum at intervals; this is the residual in the bronchial tree and does not mean fresh bleeding. Another episode of bleeding may occur after a period of hours or days necessitating further intravenous injections of the drug. In general, however, one intravenous injection of pituitrin will serve to control the most severe pulmonary hemorrhage.

The technique we have followed is to dilute 10 international units of pituitrin (1 cc. of Obstetrical Pituitrin or 0.5 cc. of Surgical Pituitrin, Parke Davis Co.) with 10 cc. of normal saline solution and, using a watch, inject this solution intravenously slowly over a 10 minute period using an accessible arm vein. The patient is kept in the supine position. During the injection the pulse rate may not change or may show only a slight increase; the blood pressure usually remains constant before and after the injection. A short time after the introduction of the drug into the blood stream the patient may complain of feeling dizzy, and the powerful vasoconstrictor action of the drug is noted in an intense pallor of the face and extremities. This may be followed by slight abdominal cramping pains and an urge to empty the bowels and bladder. A bed pan should be available. Nausea is of common occurrence towards the end of the injection and may result in the emesis of clotted blood swallowed during the course of the hemoptysis. These effects are transitory and rapidly disappear. There have been no serious untoward effects in these patients. One theoretical contraindication to its use would be in a patient with a history of angina pectoris, although we have experienced no difficulty in using intravenous pituitrin in elderly patients with advanced generalized arteriosclerosis. Several obstetricians of experience advise us that it is perfectly safe to use the drug during the first two and even during the third trimester of pregnancy if necessary to control a severe pulmonary hemorrhage. We have had no occasion to administer it under such circumstances.

The pharmacology of the action of intravenous pituitary extract in the control of pulmonary hemorrhage has not been completely studied though there is some French work on the subject.[2,3]

Case Reports

Miss. L. I. A 21 year old Italian girl was found to have far advanced acute exudative pulmonary tuberculosis in June 1947. She was placed at bed rest and started on pneumoperitoneum therapy. On this regime she did moderately well until November 12, 1947 when she began to have a series of small hemoptyses each amounting to one-half to two ounces in quantity. She continued to hemorrhage briskly over the next three days and when seen at home on November 16, 1947 was on the verge of shock.

At this time she was given 10 international units of pituitrin intravenously diluted in 10 cc. of normal saline solution. Her pulmonary hemorrhage was well controlled by this one injection and her future course has been uneventful except for one mild episode of hemoptysis in June 1948 which required nothing more than bed rest and sedation for control.

Mr. J. C. A 54 year old Italian male has had recurrent episodes of hemoptysis since 1906. In 1913 he was found to have pulmonary tuberculosis but received no treatment. In July of 1933 he entered a sanatorium with extensive active bilateral pulmonary tuberculosis which responded well to bed rest and collapse therapy. There has been no evidence of active pulmonary tuberculosis since 1938. He has bilateral upper lobe bronchiectasis as a result of the scarring and fibrosis secondary to his arrested tuberculosis. However, since this time he has had several upper respiratory infections with blood streaked sputum and occasional episodes of frank hemoptysis. The majority of his episodes of hemoptysis have required no treatment other than bed rest. On May 17, 1948 he had a hemoptysis of about 120 cc. of blood; he then entered the emergency ward of our County hospital and in spite of transfusions and the usual measures then used by us to control pulmonary bleeding he continued to have massive hemoptysis. No collapse therapy of any kind was possible; he was too dyspneic and cyanotic even to consider the use of pneumoperitoneum. We could not be sure from which upper lobe the bleeding was coming although it was believed to be from the left top. At times an emergency thoracoplasty has been done to attempt to control such bleeding but in this man it is doubtful if he could have survived such a procedure. At 1:30 a. m. on the 18th of May 1948 he was given 10 international units of pituitrin intravenously in 10 cc. of saline solution over a 10 minute period. The response was dramatic, with immediate control of the pulmonary bleeding. This injection was repeated again 12 hours later. Following this his further hospital course was uneventful and he was discharged in a few days. Again on April 19, and September 30, 1949 he had severe episodes of hemoptysis requiring hospitalization. On both occasions he received intravenous pituitrin, 10 international units in 10 cc. of normal saline solution which immediately controlled the bleeding. Since the latter date he has had no further episodes of hemoptysis requiring hospitalization or treatment.

Mrs. I. L. A 27 year old graduate nurse was awakened early in the morning of September 9, 1949 by a hemoptysis of approximately 200 cc. of bright red blood. She was seen by her family physician who carried out the usual measures. In spite of this she continued to bring up moderate quantities of blood several times daily. The bleeding continued for 48 hours at which time she received 10 international units of pituitrin slowly by vein. During the injection she noted mild abdominal cramping pain which passed within a few minutes. The pulmonary bleeding was immediately controlled until three days later when a severe episode of coughing brought on another pulmonary hemorrhage of approximately 150 cc. of blood. She was seen at home and a second injection of 10 units of pituitrin given slowly intravenously. Once more the bleeding was controlled. Following this she was hospitalized for bronchoscopy and lipiodol bronchograms which revealed bronchiectasis of the right middle and lower lobes. Thoracotomy was performed on September 27, 1949 and resection of the right middle and lower lobes was done. Pathological study

of the surgical specimen revealed the bleeding to be coming from a small bronchial artery that had eroded into the right lower lobe bronchus. There has been no further bleeding since surgery was performed.

Mrs. D. N. A 71 year old Italian female has had a productive cough for the past several years with intermittent episodes of wheezing for the past year. On August 4, 1949 following a hard coughing spell she had a pulmonary hemorrhage of approximately 400 cc. of bright red blood. She was placed at complete bed rest and treated conservatively but continued to have pulmonary bleeding over the next two days. On August 6th she had another hemorrhage of approximately 200 cc. of blood and at this time she was seen at home and given 10 international units of pituitrin intravenously in 10 cc. of saline solution. The bleeding was immediately controlled. During the injection she vomited once, with the vomitus containing much old blood. Following the injection she felt the urge to urinate. These symptoms passed in a few moments and she was much improved. Blood pressure and pulse remained normal before and after the injection. At a later date bronchoscopy revealed a normal bronchial tree, but further diagnostic studies could not be completed. There has been no further pulmonary hemorrhage.

Mrs. M. G. A 31 year old white female was found to have a thin walled cavity in the right lower lung field in July 1946. Coccidioides immitis was recovered from the sputum on animal inoculation. The cavity remained essentially unchanged and the patient was asymptomatic until June of 1948 when she had a large pulmonary hemorrhage which ceased spontaneously without treatment. Five months later on the 5th of November 1948 she again had a pulmonary hemorrhage of 200 to 300 cc. of blood that was immediately controlled by 10 international units of pituitrin given intravenously. Since this latter date the patient has had several episodes of hemoptysis with each one immediately controlled by 10 units of intravenous pituitrin administered by her husband who is a physician.

Mr. M. W. A 28 year old white male was known to have had one attack of acute rheumatic fever during childhood. In June of 1949 he had a chest x-ray film following an injury to his chest which revealed a coarsely mottled perihilar density diffusely scattered throughout each lung field and calcified nodules up to 6 mm. in diameter in both lung bases. Examination of the heart revealed the murmurs of mitral stenosis and insufficiency and aortic stenosis and insufficiency. He is considered to have rheumatic heart disease and hemosiderosis of the lungs.

He was well until January 1950 when he began to have repeated episodes of hemoptysis. Bronchoscopy at this time revealed blood oozing from both lower lobe bronchi, typical of the bleeding secondary to mitral stenosis. Tuberculin, coccidioidin, and histoplasmin skin tests were negative in dilution of 1-100. On February 10, 1950 he had a large hemoptysis of over 1,000 cc. of blood. After hospitalization, he was given 10 international units of pituitrin slowly by vein. The severe hemorrhage was immediately controlled. However, over the past six weeks he has had recurrent episodes of hemoptysis requiring a total of six injections of 10 units of pituitrin intravenously for immediate control of the bleeding. In each case the control of the severe pulmonary bleeding has been quite successful, but treatment designed to relieve the pulmonary hypertension secondary to his mitral stenosis has been ineffectual to date.

Mr. L. V. A 33 year old Filipino male was found to have far advanced pulmonary tuberculosis in May of 1948. Shortly after entering the sanatorium he began to have a series of intractable hemoptysis. On May 18, 1948 he was given five international units of pituitrin slowly intravenously and this was repeated two days later. There was no perceptible change in his bleeding pattern and the patient bled so profusely that he was practically exsanguinated and he expired as a result of hemorrhage.

This case is the only one of the series in which death resulted from continued hemorrhage following the use of pituitrin intravenously. It is felt that the fact that only five international units of pituitrin were used in this case instead of the 10 international units recommended, may have been a contributory factor to his continued bleeding and death.

SUMMARY

1) Pituitrin is the best available drug for the control of severe pulmonary hemorrhage. It must be used intravenously to be effective.

2) Untoward effects are minimal and transient if the technique described is scrupulously followed.

3) It can be used immediately for control of pulmonary hemorrhage from whatever cause. An adequate diagnosis of the pulmonary condition responsible for the hemorrhage must then be made.

RESUMEN

1) La pituitrina es la droga disponible más eficaz para el control de hemorragias pulmonares graves. Para que sea eficaz, debe administrarse por la vía intravenosa.

2) Los efectos contraproducentes son mínimos y transitorios, si se observa escrupulosamente la técnica descrita.

3) Se puede usar inmediatamente para el control de hemorragias pulmonares, no importa cual sea la causa; pero, después, debe hacerse el diagnóstico adecuado del estado pulmonar que causó la hemorragia.

REFERENCES

1 Bogen, Emil: "The Pathogenesis of Tuberculous Hemoptysis, A Clinical Pathological Investigation," *Am. J. Clin. Path.*, 2:299, 1932.

2 Emile-Weil P. and Boye: "Different Actions of Pituitrin on the Coagulation of Blood in Man and Rabbit," *Bull. Soc. Biol.*, 67:428, 1909.

3 Livon: "Different Actions of Pituitrin on the Blood of a Dog," *Bull. Soc. Biol.*, 67:648, 1909.

4 Plessinger, Virgil A. and Jolly, Paul N.: "Rasmussen's Aneurysms and Fatal Hemorrhage in Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 60: 589, 1949.

5 Rasmussen, B.: "On Hemoptysis, Especially When Fatal, in Its Anatomical and Clinical Aspects," translated by W. D. Moore, *Edinburgh M. J.*, 14:385, 1868.

6 Rist, Edouard: "Treatment of Hemoptysis by Intravenous Injection of

Pituitrin," *Bull. and Mem. of the Soc. of Med. of the Hospital of Paris I*, 1:776, 1913.

7 Rist, Edouard: "Les Symptoms de la Tuberculous Pulmonaire," *Masson et Cie*, p. 110, 1943.

8 Savy, Paul: "Treatment in Therapeutic Medicine," *Masson et Cie*, 2: 1447, 1940.

9 Wiggers, Carl J.: "Physiological Investigation of the Treatment of Hemoptysis," *Arch. Int. Med.*, 8:17, 1911.

10 Wiggers, Carl J.: "The Physiology of the Pituitary Gland and the Actions of Its Extracts," *Am. J. M. Sci.*, 141:502, 1911.

The Efficiency of Different Laboratory Examinations in the Diagnosis of Pulmonary Tuberculosis*

DAIKICHI HATA, JR.,† HOMER D. VENTERS, JR.‡ and MARTIN M. CUMMINGS, M.D.‡‡
Atlanta, Georgia

Patients with symptoms, signs, or x-ray findings suggestive of pulmonary disease present the clinician with the problem of differential diagnosis. Although, with the proper use of the tuberculin test and serial roentgenograms, the presence of tuberculous infection may be ruled out, none the less, it is difficult to establish the presence of active pulmonary tuberculosis. Many types of laboratory examinations are available for the latter purpose, such as microscopic search for acid-fast bacilli in sputum and other body fluids and search for tubercle bacilli either by cultivation or by animal inoculation.

Examination of gastric washings from patients suspected of having pulmonary tuberculosis, who either produce no sputum or have bacteriologically negative sputum, has long been known as a sensitive test for detecting the presence of tubercle bacilli. Laryngeal swabs also have been reported to be useful for bacteriological diagnosis.

That results depend entirely on the methods of handling the specimens and on the techniques employed in isolating tubercle bacilli from them must be emphasized.

The present investigation was instituted in an attempt to determine which pathological materials are most useful in the diagnosis of tuberculosis, and which methods are most efficient in isolating tubercle bacilli.

Clinical Material

Observations were made on patients in the Lawson Veterans Administration Hospital and U. S. Veterans Administration Hospital No. 48, Atlanta, Georgia. A total of 107 patients were examined; all were male veterans of World Wars I and II with an age range of 20 to 68 years, the average being 35.9 years.

*Study was performed at the Tuberculosis Evaluation Laboratory, Communicable Disease Center, Public Health Service, Atlanta, Georgia.

†Assistant Sanitarian (R).

‡‡Medical Research Laboratories, Lawson Veterans Administration Hospital, Chamblee, Georgia, and Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Procedures

Four different specimens—sputum, gastric contents, laryngeal swab, and urine were collected from each patient who had been fasting for 12 to 16 hours.

I. *Centrifuged and non-centrifuged sputum specimens.*

The first morning sputum specimens were expectorated and collected in wide-mouthed, screw-capped bottles of two-ounce capacity. Without delay each specimen was placed in the paint conditioner and homogenized for five minutes. A portion of the specimen was then smeared on a clean glass slide for staining. The remaining portion was divided into two parts designated for tabulation as A and B and these were placed in sterile, screw-capped test tubes.

To part A was added an equal volume of 4.0 per cent sodium hydroxide. The specimen was then shaken for 10 minutes in the paint conditioner and allowed to stand for an additional 30 minutes. Without further centrifugation a nitrazine indicator paper was added, and the specimen was neutralized by adding 5.0 per cent sulfuric acid drop by drop. The total exposure time of the specimen to sodium hydroxide was approximately 40 minutes. After neutralization 0.1 cc. of the homogeniezd and neutralized specimen was inoculated directly onto each of two tubes of Jensen's modification of Lowenstein's medium. These tubes were placed in a horizontal position for 24 hours.

Part B was mixed with an equal volume of 4.0 per cent sodium hydroxide, shaken for 10 minutes in the paint conditioner, allowed to stand for 10 minutes, and centrifuged for 20 minutes at 3,000 RPM. The total exposure time of the specimen to sodium hydroxide was again approximately 40 minutes. The supernatant was decanted, indicator was added and the residue was neutralized with 5.0 per cent sulfuric acid. Two tubes of Jensen's modification of Lowenstein's medium were then inoculated directly with a Pasteur pipette.

II. *Diluted and undiluted gastric contents.*

Gastric specimens were collected from the fasting stomach in every instance. Both the Levine tube and the larger French No. 30 gastric tube were used with mineral oil as lubricant. The tubes were not iced routinely.

Ten ml. of the undiluted stomach contents were first aspirated and placed in a sterile screw-topped test tube. Then 100 to 150 ml. of sterile distilled water were introduced, and the diluted gastric contents were aspirated and placed in a sterile container.

For the additions and withdrawals of fluids through the Levine tube, a glass syringe of 50.0 ml. capacity was found most satisfactory.

In preparation for inoculation of culture media the 10.0 ml. of undiluted gastric specimen was mixed with an equal volume of 4.0 per cent sodium hydroxide, shaken for 10 minutes in a paint conditioner, and then centrifuged for 20 minutes at 3,000 RPM. The supernatant was decanted, a nitrazine indicator paper was added, and the residue was neutralized with 5.0 per cent sulfuric acid. Two tubes of Jensen's modification of Lowenstein's medium were inoculated. This procedure is designated as C in the tabulation of experimental results.

The diluted gastric specimen, varying from 100 to 150 ml. in volume, was first shaken and homogenized for five minutes in a paint conditioner. The specimen was then divided into three, sterile, screw-topped test tubes.

Two of the three tubes were then directly centrifuged at 3,000 RPM for 15 minutes. The supernatant was poured off, and the residues were pooled before being treated with sodium hydroxide.

The third tube was treated with a saturated solution of alum (aluminum-potassium sulfate) and neutralized with 4.0 per cent sodium hydroxide. The flocculent precipitate formed was collected by centrifugation at 3,000 RPM for 15 minutes. The supernatant was decanted and discarded.

The residues of both concentration procedures (homogenization and centrifugation of diluted washings (D), and addition of alum and NaOH followed by centrifugation (E) were treated with an equal volume of 4.0 per cent sodium hydroxide, shaken for 10 minutes in the paint conditioner, and then centrifuged again at 3,000 RPM for 15 minutes. The supernatants were poured off, nitrazine indicator paper was added, and the residues were neutralized with 5.0 per cent sulfuric acid. Two tubes of Jensen's modification of Lowenstein's medium were inoculated from each preparation. The results of the procedure involving concentration by centrifugation are designated for tabulation as D and those of the alum treatment as E.

III. *Urine specimens.*

The first morning voiding of urine was collected in a sterile container. This specimen was allowed to stand for three hours, the supernatant was decanted, and the sediment was divided into three sterile screw-topped test tubes. Two of the tubes were immediately centrifuged at 3,000 RPM for 15 minutes. The third tube was treated with a saturated alum solution, and the flocculent material formed was concentrated by centrifuging at 3,000

RPM for 15 minutes. If the urine was acid and flocculation occurred, neutralization with sodium hydroxide promoted precipitation.

After centrifugation the supernatant was decanted, and the residues of the first two tubes were pooled. To each tube was added an equal volume of 4.0 per cent sodium hydroxide. The specimens were then shaken for 10 minutes in a paint conditioner and then centrifuged for 15 minutes at 3,000 RPM. The supernatant was decanted, nitrazine indicator paper was added, and the residues were neutralized with 5.0 per cent sulfuric acid. Each neutralized specimen was inoculated onto two tubes of Jensen's modification of Lowenstein's medium. The results of the procedure involving concentration by centrifugation are designated for tabulation as F and those of the alum treatment as G.

IV. *Laryngeal swabs.*

Two laryngeal swabs were collected from each patient. The swabs were made of non-absorbent cotton extracted for five hours with ether with the Soxhlet apparatus, dried, and threaded through a small loop of wire of a gauge which will resist slight bending. They were sterilized and moistened with sterile distilled water immediately before use.

The tongue of the patient was firmly held between the folded edges of a four by four inch gauze pledget with the left hand while the swab was inserted as near the larynx as possible with the other hand. The patients were encouraged to cough on the swab during the procedure. Each swab was treated in a different manner.

1) By use of a sterile Petri dish, a sterile pair of scissors and a sterile forcep, one of the two swabs was removed from the wire holder, divided into two parts and placed in a single sterile screw-top test tube. Ten ml. of 2.0 per cent sodium hydroxide were then added, mixed, and the specimen was allowed to stand for 10 minutes. This was followed by centrifugation for 15 minutes at 3,000 RPM. The supernatant was decanted, and the residue including the two pieces of the swab was neutralized by filling the tube with Petrik's buffer (pH 6.55). After shaking, the tubes were centrifuged again at 3,000 RPM for 15 minutes. The supernatant was then decanted and discarded. Two tubes of Jensen's modification of Lowenstein's medium were inoculated by smearing the surface with a piece of the swab which was then left in the bottom of the tube of culture. The results of this procedure are designated as H.

2) With sterile technique the second swab was removed from its wire holder and placed in a sterile screw-cap test tube. Five ml. of 3.0 per cent hydrochloric acid were then added, and the

TABLE I

Specimen	Procedure	Total	POSITIVE Number	POSITIVE Per cent	NEGATIVE Number	NEGATIVE Per cent	CONTAMINATED Number	CONTAMINATED Per cent
Sputum	A (not conc.)	130	46	35.4	82	63.0	2	1.6
	B (conc.)	130	49	37.7	80	61.5	1	0.8
Gastrics	C (NaOH, not diluted)	130	57	43.9	70	53.7	3	2.4
	D (NaOH, diluted)	130	51	39.2	77	59.2	2	1.6
	E (alum ppt.)	130	48	37.0	81	62.2	1	0.8
Urines	F (NaOH)	130	2	1.5	127	98.2	1	0.8
	G (alum ppt.)	130	3	2.3	127	97.7	0	0.0
Laryngeal swabs	H (NaOH)	130	22	16.9	96	73.9	12	9.2
	Hi* (NaOH)	31	2	6.5	22	88.1	7	5.4
	I (HCl)	31	0	0.0	31	100.0	0	0.0

*Part of series H.

specimen was shaken in the paint conditioner for five minutes. The swab was then removed with sterile technique and discarded, and the remaining solution was left standing at room temperature for 45 minutes. This was followed by centrifugation at 3,000 RPM for 15 minutes. The supernatant was decanted, nitrazine indicator paper was added, and the residue was neutralized with 4.0 per cent sodium hydroxide. Two tubes of Jensen's modification of Lowenstein's medium were inoculated. The results of this procedure are designated for tabulation as I.

All of the cultures were incubated at 37 degrees C. for six weeks and were read at weekly intervals. Cultures showing no growth after six weeks were considered negative.

Characteristic colonies were tested for acid-fastness before being recorded as *Mycobacterium tuberculosis*. Atypical colonies were subcultured and inoculated into animals for further study.

Results of Experimental Procedures

The series of procedures A through H were completed 130 times. Procedure I (laryngeal swab treated with HCl) was completed only 31 times. The 31 companion swabs which were treated with NaOH are designated Hi. The results of all tests are shown in Table I.

It can be seen from the tabulated data that the greatest number of positives was obtained from gastric washings cultured after NaOH treatment (C). The least productive procedure in this series of tests was the culture of the urine. This is to be expected since the patients had primarily pulmonary lesions. Cultures of sputum specimens gave a high percentage of positives as expected but results from cultures of laryngeal swabs were poor (17 per cent positive as compared to 44 per cent positive by gastric lavage).

Comparison of Smears and Two Types of Sputum Cultures

In comparing the results of direct smears of sputum made after homogenization and the cultural procedures A (homogenized but uncentrifuged and non-concentrated sputum) and B (homogenized

TABLE II

Smears and Cultures

Procedure	Total	Per cent Positive	Number Positive	Number Negative	Number Contaminated
Culture A (not conc.)	130	35.4	46	82	2
B (conc.)	130	37.7	49	80	1
Smear	130	21.7	28	102	0

sputum concentrated by centrifugation), it was found that 21.7 per cent of the direct smears were positive for acid-fast bacilli whereas 35.4 per cent were positive by cultural procedure A and 37.7 per cent by procedure B. Table II presents the data on comparison of direct smears and procedures A and B.

Two direct smears of homogenized sputum were considered doubtful; both were positive by cultural procedures A and B. It seems evident that the culture is more sensitive than the direct smear in detecting tubercle bacilli in sputum.

Gastric Washings

In comparing the procedures used in treating gastric washings it was found that 57 (43.9 per cent) of the 130 undiluted gastric contents produced positive cultures; 51 (39.2 per cent) of the same gastric contents were positive by procedure D (diluted and concentrated by centrifugation); 48 (37.0 per cent) by procedure E (concentrated by alum flocculation). The results are shown in Table III. The difference between results of procedures C, D and E are not significant.

In 18 cases the gastric contents were found positive by one or all of the cultural methods used while the sputum cultures were negative. Conversely, in five cases one or both methods of sputum cultures were positive while all procedures used in culturing gastric contents produced negative results.

In the instance where the series was repeated twice and three times the gastric contents were positive in every attempt whereas the other procedures were negative. It is clear that examination of gastric contents under proper conditions is a most sensitive method for detecting tubercle bacilli in pulmonary tuberculosis.

Comparison of Urine Specimens

Of the 130 urine specimens collected only two were found positive by cultural procedure F (concentrated by centrifugation) and three by procedure G (concentrated by alum flocculation). Only

TABLE III

Results of the Examination of Gastric Contents

Procedure		Total	Per cent Positive	Number Positive	Number Negative	Number Contaminated
C	NaOH (undiluted)	130	43.9	57	70	3
D	NaOH (diluted)	130	39.2	51	77	2
E	Alum ppt.	130	37.0	48	81	1

one of the specimens found positive by both procedures. This was obtained from a patient with a clinical diagnosis of urogenital tuberculosis.

Comparison of Laryngeal Swabs

In 31 instances in which procedures Hi (laryngeal swab neutralized with Petrik's buffer and I (laryngeal swab treated with hydrochloric acid and neutralized with sodium hydroxide) were performed together, procedure I gave completely negative results. Examination of 130 laryngeal swabs by procedure H yielded 23 (16.8 per cent) positive results. In all cases either the gastric lavage, or the sputum specimen, or both, were found to be positive when the laryngeal swab was found positive. The results of swab examinations are tabulated in Table IV. The differences between procedures I and Hi, H and Hi are of no significance, but the difference between results of examination of swabs and sputum, or gastric specimens, is of evident significance.

Discussion

It appears to us that cultural examination of gastric lavage is the most efficient method of obtaining bacteriological evidence of pulmonary tuberculous infection. Meunier[1] in 1898 first introduced this method to establish the diagnosis of tuberculosis in children who swallow their sputum. Armond-Debille[2] in 1927 demonstrated the value of gastric lavage in diagnosing tuberculosis in adults who had repeatedly negative sputum examinations. However, it was later (1941) pointed out by Roper and Ordway[3] that the result of examining a single gastric lavage was insufficient to rule out the presence of tuberculosis and that a series done on consecutive days appreciably increased the percentage of positive results. This is true of almost any bacteriological examination and is virtually self-evident.

It must be pointed out that smears of gastric washings are totally unreliable because of frequent presence of non-pathogenic

TABLE IV

Results of Examination of Laryngeal Swabs

Procedure		Total	Per cent Positive	Number Positive	Number Negative	Number Contaminated
H	NaOH	130	16.9	22	96	12
Hi	NaOH	31	6.5	2	22	7
I	HCl	31	0.0	0	31	0

acid-fast bacteria found in stomach contents. Holloway and Cummings[4] recently described the error of finding acid-fast saprophytes in stomach contents of normal individuals.

It should also be remembered that gastric washings should be processed for cultivation immediately after collection of the specimen. Floyd and Page[5], Sprick and Towey,[6] Schwarting[7] and others have demonstrated that aging of the specimen adversely affects the viability of tubercle bacilli in gastric washings. This deleterious effect has been attributed by some to the free hydrochloric acid whereas others believe that enzymes present in the gastric juice are responsible. If these sources of error are avoided, cultures and animal inoculation of gastric lavage appear to be superior to other methods of establishing a positive diagnosis of pulmonary tuberculosis and evaluating the progress of patients with this disease.

It was most interesting to find that sputum cultures made without centrifugalization and concentration of the sputum were about as efficient as those prepared after centrifugalization and concentration. Feldman and Hanks[8] and Spendlove et al.[9] have questioned the value of centrifugalization, since tubercle bacilli have a specific gravity which is often less than that of the digested sputum. This would indicate that often the bacilli may be discarded in the supernatant fluid. Recently we have been cultivating tubercle bacilli from the supernatant as well as from the sediment and occasionally the former is positive whereas the latter may be negative.

The use of laryngeal swabs for culture has been recommended in situations where gastric lavages are not practicable or feasible. Nassau[10] reported a high percentage of positive cultures from laryngeal swabs of patients with little or no sputum. Sula,[11] using a fluid medium for culture, has also reported positive results from 13.5 to 28.8 per cent of patients whose sputum is negative on microscopic examination. Although our series is small (31 attempts) it appears to us that the laryngeal swab is not as effective as gastric lavage for isolation of tubercle bacilli, but may be of some value when other methods are not applicable.

From time to time it has been suggested that tubercle bacilli may be excreted in the urine of patients with pulmonary tuberculosis. It has been postulated that a transient bacteremia occurs occasionally and that during these periods one may recover tubercle bacilli in the urine. Three positive urine cultures were obtained from patients without clinical evidence of urogenital tuberculosis. This might suggest the above hypothesis, but one must remember that urogenital tuberculosis may exist without clinical evidence of infection.

The greater efficiency of cultivation from sputum as a diagnostic method as compared with direct microscopic methods, is borne out by the finding of 15 per cent positive by this method when smear preparations of the same pathological material were negative. It has been estimated that between 10,000 and 100,000 bacilli per ml. of sputum must be present before the microscopist has a reasonable chance of finding them. Therefore, it is not safe to consider a patient "bacillus free" unless adequate cultural studies have been made.

Banyai[12] has already pointed out the value of gastric lavage in pulmonary as well as extrapulmonary tuberculosis. In his excellent review of this subject he has stressed the simplicity of the procedure and its importance as a gauge in the clinical management of tuberculous patients. The results of this study lend weight to his ideas. It is our impression that the procedure is not used often enough as a diagnostic method. It is suggested that no patient with symptoms or signs of pulmonary disease be considered free of tuberculosis infection unless three serial gastric washings collected at weekly intervals are negative for tubercle bacilli by cultivation and/or animal inoculation.

SUMMARY

1) One hundred and seven patients with signs or symptoms of pulmonary disease were studied by attempting to cultivate tubercle bacilli from sputum, gastric washings, laryngeal swabs and urine.

2) Of the gastric specimens 43.9 per cent were found positive by culture, as compared with 37.7 per cent of sputa, 16.9 per cent of laryngeal swabs and 2.3 per cent of urine specimens.

3) Concentration of the sputum specimens increased the number of positives by only 2 per cent.

4) Cultures of sputum were positive in 20 per cent of cases in which smear examinations of sputum were negative.

Acknowledgements: The authors wish to thank Dr. Max Michael of Lawson Veterans Administration Hospital and Dr. Gerson Hollander of Veterans Administration Hospital No. 48 for assisting us in obtaining the clinical material which this study required. We are also indebted to Dr. Paul Beeson and Dr. Martin Frobisher, Jr. for their suggestions in preparation of the manuscript.

RESUMEN

1) En un estudio de 107 pacientes con signos y sintomas de neumopatía se trató de cultivar bacilos tuberculosos en el esputo, el lavado gástrico, en secreciones obtenidas en la laringe y en la orina.

2) De los espécimenes gástricos el 43.9 por ciento fueron posi-

tivos en el cultivo, comparado con el 37.7 por ciento en el esputo, el 16.9 por ciento en las secreciones de la laringe y el 2.3 por ciento en los espécimenes de la orina.

3) La concentración del esputo sólo aumentó por un dos por ciento el número de espécimenes positivos.

4) Los cultivos del esputo fueron positivos en 20 por ciento de los casos en los que los exámenes del frote del esputo fueron negativos.

REFERENCES

1 Meunier, H.: "Bacteriological Examination of the Gastric Contents in the Diagnosis of Pulmonary Tuberculosis in Children," *Presse Med.*, 2:81, 1898.
2 Armond-Deville, P. F. and Vibert, J.: "Bacteriological Diagnosis of Pulmonary Tuberculosis in Infants by the Examination of the Stomach Contents," *Presse Med.*, 35:402, 1927.
3 Roper, W. H. and Ordway, W. H.: "Gastric Lavage in Adults with Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 43:543, 1941.
4 Holloway, J. and Cummings, M. M.: "An Evaluation of a Method of Gastric Lavage," *Am. Rev. Tuberc.*, 60:228, 1949.
5 Floyd, C. and Page, C. C.: "The Action of Artificial Gastric Juice and Duodenal Secretions on Tubercle Bacilli," *Am. Rev. Tuberc.*, 48:174, 1943.
6 Sprick, M. and Towey, J. W.: "Isolation of Mycobacterium Tuberculosis from Gastric Contents Neutralized after Varying Periods," *Pub. Health Rep.*, 61:648, 1946.
7 Schwarting, V. M.: "The Action of Gastric Content on Tubercle Bacilli," *Am. Rev. Tuberc.*, 58:123, 1948.
8 Feldman, H. A. and Hanks, J. H.: "Analysis of Present Methods of Collecting Tubercle Bacilli from Urine," *Proc. Soc. Exp. Biol. and Med.*, 40:385, 1939.
9 Spendlove, G. A., Cummings, M. M. and Patnode, R. A.: "Demonstration of Tubercle Bacilli in Sputum Smears. Selection of Choice Particles Compared with Various Sodium Hydroxide Concentration Techniques," *Pub. Health Rep.*, 64:18, 1949.
10 Nassau, E.: "The Culture of Tubercle Bacilli from Laryngeal Swabs," *Proc. Royal Soc. Med.*, 34:397, 1944.
11 Sula, L.: "Deep Swab Culture; A New Method for Cultural Demonstration of Tubercle Bacilli," *Acta Tuberc., Schandinav.*, 21:160, 1947.
12 Banyai, A. L.: "Clinical Value of Examination of the Gastric Contents for Tubercle Bacilli," *Am. J. of Med.*, 4:836, 1948.

Chest Injuries in Civilian Practice*

EDWARD F. SKINNER, M.D., F.A.C.S.,
DUANE CARR, M.D., F.A.C.S., F.C.C.P.,
CHARLES R. KESSLER, M.D. and WM. E. DENMAN, M.D.†
Memphis, Tennessee

A number of excellent articles were written during and immediately after World War II dealing with the management of penetrating wounds of the thorax and intrathoracic viscera. Less consideration has been given to the types of injury more commonly encountered in civilian practice. We refer particularly to crushing injuries sustained by the chest wall, lungs and heart as a result of automobile and aeroplane accidents. We will attempt to outline the physiologic principles governing the management of both penetrating and crushing injuries, with special attention paid to averting the common complications which are often associated with them.

Penetrating Wounds of the Chest Wall and Lungs

For the purpose of directing emergency treatment, penetrating wounds of the chest wall are divided into those which are "sucking" (drawing in and/or expelling air with each respiration) and those which are "closed" (having sealed themselves).

Sucking wounds, or those with an open hole in the chest wall, have an especial physiologic significance. A series of four untoward events occurs in the presence of a sucking wound: 1) collapse of the homolateral lung, 2) shift of the mediastinum toward the contralateral side, 3) swinging mediastinum, and 4) "pendleluft," or exchange of air between the two lungs. When the chest wall is opened, air under atmospheric pressure rushes into the thorax to neutralize the negative pressure of the pleural cavity. This permits the naturally contractile homolateral lung to collapse. At this stage one hemithorax is then at atmospheric pressure while the contralateral hemithorax is under negative pressure. As the mediastinal walls are but flimsy structures, the mediastinum shifts to the contralateral side *thereby partially neutralizing the negative pressure in the "good" side*. A swinging mediastinum which shifts with the respiratory efforts of the patient makes it still more difficult to develop sufficient negative pressure to draw

*Presented at the 6th Annual Meeting, Southern Chapter, American College of Chest Physicians, Cincinnati, Ohio, November 15, 1949.

†From the Departments of Surgery and Medicine, University of Tennesse College of Medicine, Memphis, Tennessee.

air into the one usable lung. In this state it is mechanically easier for air within the lungs to be exchanged from one lung to the other than it is to be expelled through the trachea, and exchanged for fresh air brought in through the upper respiratory passages. The air exchanged from lung to lung becomes progressively more devoid of oxygen and laden with carbon dioxide.

Thus a patient with an open or sucking wound in the chest wall soon goes into shock, a physiologic shock which has no bearing upon blood loss, splanchnic vascular dilatation, anoci-association, or to blood sludge formation. No amount of blood plasma, blood transfusions, or other standard shock therapy will remedy this condition until the physiologic disturbance itself is corrected.

The obvious emergency treatment of such a patient begins with *closing the hole immediately*, which will stabilize the mediastinum and stop the exchange of air between the two lungs. Then removal of a part of the air in the homolateral hemithorax will provide the patient with sufficient breathing capacity to sustain life. This accomplished, management of such a patient then follows the same pattern as other penetrating wounds of the chest.

Penetrating wounds caused by an ice pick, flying glass, small fragments of metal, or small caliber bullets usually seal themselves promptly following injury. They are accompanied, however, in the majority of instances by a laceration of the lung which results in a hemopneumothorax and often subcutaneous emphysema. The hemopneumothorax may not become apparent immediately, and may even fail to be demonstrated upon an x-ray film made within an hour of the injury. This is a point worth noting, for there is a temptation when the skin laceration is small and the x-ray film negative, to assume that the lung has not been injured. This can prove to be a fatal assumption unless the patient is hospitalized and a truly sharp observation maintained over him. A slowly developing hemopneumothorax is well tolerated by a patient until the critical level of respiratory capacity is reached, when, if he is at home or unattended, he goes suddenly into a state of profound shock and extremis.

The patient with a closed chest wall wound who is dyspnoic, cyanotic, and in shock is best treated by immediate aspiration of air or blood, or both, from the affected hemithorax. General measures to combat shock are likewise applied, including nasal oxygen, Trendelenburg position, and intravenous irradiated plasma and blood. Body heat should be conserved but external application of heat appears to be unphysiologic in that the contracted peripheral vascular bed is of assistance in maintaining blood pressure, and the cooler tissues with a lower metabolic rate demand less oxygen. When heat and stimulation are desired, the old and almost for-

gotten practice of giving a pint of warm coffee by enema is still useful.

Immediate aspiration of the chest is not necessary in the patient whose breathing is not unduly labored or in whom no cyanosis appears. In fact, it is better to allow 24 hours to elapse, permitting the associated lung laceration to become sealed, before aspirations

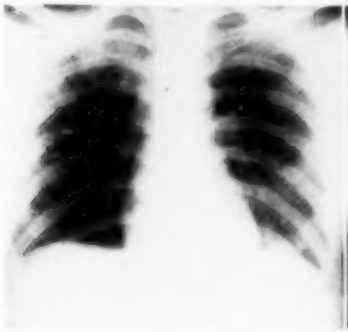


FIGURE 1

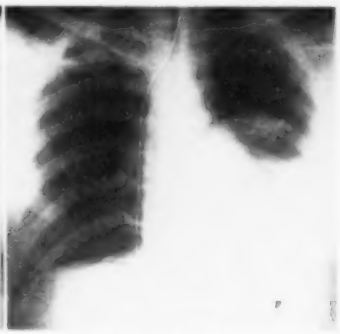


FIGURE 3

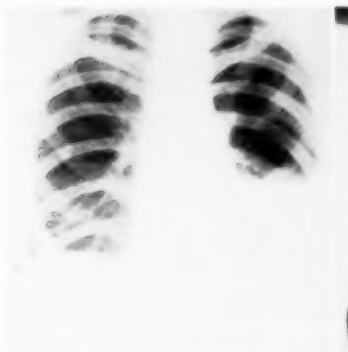


FIGURE 2

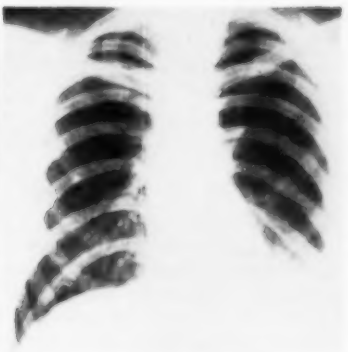


FIGURE 4

Figure 1, Case 1: Mr. S.McG. On September 17, 1949 this film was made immediately after admission to the hospital. This boy attempted suicide by shooting himself through the left upper abdomen and lower chest with a 22 caliber bullet. The admission film appears relatively normal but at exploratory laparotomy penetrating wounds of the stomach and diaphragm were seen and repaired from below.—*Figure 2, Case 1:* Film made eight hours after the admission film shows a 40 per cent collapse of the left lung by pneumothorax with a small amount of bloody fluid as well in the pleural space.

Figure 3, Case 1: Film made on September 24, 1949 shows continued improvement of the left chest injury, but persistent formation of blood in the pleural space necessitated frequent aspirations of the bloody fluid.—*Figure 4, Case 1:* Film made on September 30, 1949 reveals a practically normal chest shortly before the patient was discharged from the hospital.

are begun. It is necessary, however, to begin aspirations of the pleural cavity when air, blood or serum are present 24 hours after injury. The sooner the lung is reexpanded and the pleural cavity dried out (and kept dry) the less likely it is that an empyema will develop or thickening of the pleura take place. The presence of even a small amount of blood (which is an irritant to the pleura) will cause pleural effusion to develop for many days. This fluid is an excellent culture medium for the organisms which are usually carried into the pleural cavity by the penetrating instrument. This effusion should therefore be evacuated and a combination of penicillin (100,000 units) and streptomycin (1.0 Gram) returned at the close of each aspiration. Only when the lung is 1) at least 90 per cent expanded, 2) the pleural cavity dry, and 3) the temperature normal for three consecutive days can the patient be safely discharged from the hospital.

The importance of keeping the pleural cavity dry becomes apparent when one considers the layer of fibrin which rapidly develops on the pleural surfaces when they are in contact with blood or serum. This fibrin later organizes into a firm sheet, restricting the motion of the chest wall and diaphragm, and limiting the expansibility of the lung. Even should such a patient eventually recover, the function of the affected lung is greatly impaired, if not totally abolished. Furthermore, when infection is present, this fibrin harbors colonies of pathogenic organisms which are beyond the reach of the body's normal defense mechanisms. For these reasons a patient whose aspirations have been neglected will later require decortication of his lung and chest wall.

Case Reports

Case 1: S. McG. This 22 year old male shot himself in the chest with a .22 rifle on September 17, 1949. The night of admission splenectomy was performed and a penetrating bullet wound of the stomach and diaphragm repaired from below the diaphragm.

The first chest film on admission showed a pleural reaction on the left (Fig. 1) but a film eight hours later (Fig. 2) revealed left pneumothorax with a small amount of blood in the pleural space. Fairly large amounts of blood were aspirated from the left pleural space on two or three occasions (Fig. 3) after which the patient made an uneventful recovery and was discharged home on October 1, 1949 (Fig. 4).

Case 2: B. G. This young Arkansas State Policeman was shot with a .38 caliber bullet on August 29, 1949. The bullet entered the right chest posteriorly near the scapula, transected the spinal cord at the level of T-6 and came to rest in the left posterior chest. Following the injury, the patient developed paraplegia with anesthesia below the nipple level, and right hemothorax.

Admission chest film (Fig. 5) showed a moderate right hemothorax, and a film eight hours later (Fig. 6) showed a 40 per cent collapse of the right

FIGURE 5

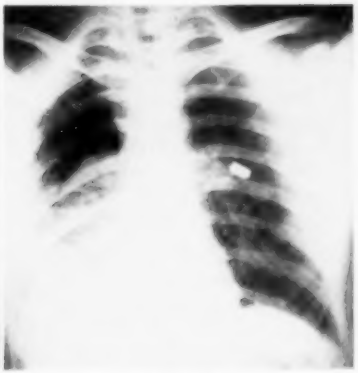


FIGURE 6

FIGURE 7

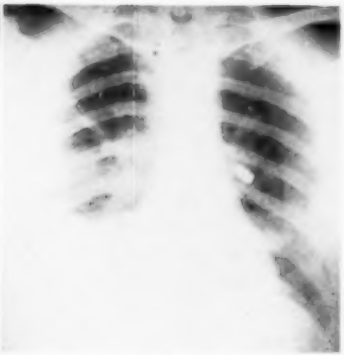


FIGURE 8

Figure 5, Case 2: Mr. B.G. Film taken on admission following gun shot wound of the chest, taken in the supine position, shows a fairly massive right hemothorax.—*Figure 6, Case 2:* Film taken eight hours later. The blood has been aspirated from the right pleural space but there is now a 50 per cent collapse of the lung by pneumothorax. Moderate amounts of air and fluid were aspirated from the right chest daily for the next few days.

Figure 7, Case 2: August 29, 1949. The next day the patient's condition became worse and an emergency chest film showed complete atelectasis of the left lung with a moderate sized right hemothorax still present. The patient was immediately turned on his right side and inhalations of carbon dioxide given as he was encouraged to cough vigorously. Several ounces of bloody sputum were expectorated. Again the right pleural space was aspirated of bloody fluid and a film made (*Figure 8*) three hours later on the same day (August 29, 1949) shows complete clearing of the atelectasis of the left lung and the patient's clinical improvement was as dramatic. His convalescence from this point was relatively uneventful and he was transferred a few days later to Kennedy General Hospital for further therapy for his paraplegia.

lung by pneumothorax with a small amount of fluid in the base. Film the following day (Fig. 7) showed atelectasis of most of the left lung. The patient was turned on his right side and made to cough forcibly and given CO2 inhalations. He succeeded in raising several ounces of thick, bloody sputum. Film three hours later showed almost complete clearing of the atelectasis of the left lung (Fig. 8). On September 10, 1949 his condition was much improved and he was transferred to Kennedy Veterans Hospital for further convalescence.

Crushing Injuries to the Chest Wall

Crushing injuries such as are sustained in automobile accidents, aeroplane crashes and industrial accidents are frought with as serious potentialities as are penetrating wounds of the chest. Because of more pain in these injuries there is an even greater tendency for the patient to avoid deep breathing and coughing, a greater desire for sedation, and the hazard of stasis of bronchial secretions with resulting atelectasis, pneumonitis, or both is increased. Pneumothorax is often produced by laceration or puncture of the lung by fractured ribs at the moment of impact. When multiple ribs are doubly fractured, as they often are, in the anterior and posterior axillary lines, a flail chest results which dangerously impairs the mechanics of respiration. This becomes apparent as paradoxical motion of the chest wall when respiratory movement is observed.

Paradoxical motion of the chest wall *must be immediately controlled* by firm adhesive strapping over pads, even though it means compressing and immobilizing the affected side. Better yet, especially when both sides are involved, the patient should be placed in a respirator.

The pneumothorax or hemopneumothorax resulting from a crushing injury of the chest wall is managed essentially in the same fashion as is this complication when associated with a penetrating wound of the chest wall. When a lung continues to leak air so that occasional or daily aspirations are inadequate to control the pneumothorax, an intercostal catheter may be placed in the pleural cavity and connected to a water-trap bottle, with or without mechanical suction for a period not to exceed 48 hours. If the leak continues after 48 hours, the catheter should be inserted in a new location in the chest wall. This should be done to prevent skin bacteria being drawn into the pleural space. Should mechanical suction be employed, a safety device must be used to prevent the development of pressure in excess of −15 cm. of water.

The high mortality rate associated with these injuries is in large part due to complicating "pneumonia." The problem is to relieve the patient's pain, promote bronchial drainage, and yet avoid the use of sedatives in a quantity which will render the sputum dif-

ficult to raise. To this end intercostal nerve block with procaine hydrochloride is effectively employed. The patient is preferably maintained in the Trendelenburg position to promote bronchial drainage, expectorants are given freely, the fluid balance is maintained, frequently turned, and coughing is forced every two hours while awake. Sedation is kept at a minimum consistent with reasonable comfort. In extreme cases, for patients with "wet" bronchi, and especially those unconscious, endotracheal suction is employed, and on occasion even bronchoscopy. Prophylactic penicillin is usually employed.

Ileus

One complication of injuries to the chest is so common, so easily overlooked, and so serious that it deserves special attention. At any time from a few minutes to a few days following a chest injury, the patient may develop ileus, with atony of the bowel and dilatation of the stomach. It is accompanied by sweating, clammy extremities, occasionally gray cyanosis, and a greater or lesser degree of shock. *The abdomen may not appear distended.* If the patient vomits, the vomitus is likely to be profuse, watery and often contains black material. Auscultation of the abdomen reveals no peristaltic sounds. This grave complication is readily overcome by using a Wangensteen suction, a rectal tube, and an alimentary tract stimulant such as prostigmine.

Traumatic Diaphragmatic Hernia

The person who is struck by a car, or over whose abdomen a vehicle has run, is likely to sustain traumatic rupture of his diaphragm with herniation of a portion of the abdomen contents into the pleural cavity. The abnormally high intra-abdominal pressure may tear the diaphragm away from its attachments, or a rent may occur through a weak segment of its dome. The physical signs in such a chest are those of consolidation or fluid. Occasionally sounds of peristalsis in the chest can be detected. The x-ray films can be difficult to interpret, especially if the stomach itself is in the pleural cavity and filled with air and fluid, giving the appearance of localized hydropneumothorax. However, the hernia can usually be detected if the possibility of its presence is suspected. The dome-shaped upper border of the "pneumothorax" or the loculated appearance of fluid and gas in the intestines in the chest are sufficiently striking in most instances to cause further studies to be carried out before inserting an aspirating needle.

There is general agreement among surgeons that prompt surgical intervention yields the best results in these cases. As soon as the

patient is brought out of shock and the upper gastro-intestinal tract deflated with Wangensteen suction and an adequate supply of blood is available, the diaphragm should be explored and repaired. The choice of a transthoracic approach versus the abdominal approach depends upon the requirements of the individual patient in regard to possible visceral damage in either the chest or abdomen. The diaphragm itself can be repaired from either side.

The Contused Heart

Crushing injuries of the chest often result in compression of the heart between the sternum and the spine with contusion of the myocardium, and may or may not be accompanied by rib fractures.

Such an injury is especially common in the driver of an automobile whose car hits an immovable obstacle, throwing him violently against the steering post. Other patients have received this injury, when, for instance, caught between the tailgate of a truck and a loading platform. It is worthy of note that the flexible cartilages permit the sternum to be depressed to the bodies of the vertebrae and the heart is squeezed between these two bony structures.

There usually is little to be found on physical examination to indicate that the heart has been damaged. It is advisable in any case in which the history suggests the possibility of cardiac contusion to obtain a portable electrocardiogram within the first 24 hours following admission to the hospital, repeating the electrocardiogram 48 to 72 hours later. If the myocardium is contused, the first electrocardiogram may be entirely normal, while the second one shows definite changes similar to those seen in an acute coronary infarct.

The patient with contused myocardium may die without warning as the damaged area in the myocardium suddenly gives way. One such patient of our acquaintance was driving his car when it hit a tree. He stepped from behind the wheel, refused offers of assistance from spectators, walked a few steps and fell dead. Another such patient expired on his way to the hospital elevator after being treated in the hospital for 10 days for fractured ribs. A bicyclist was struck by a car and died several hours after a successful repair of his traumatic diaphragmatic hernia. Autopsy showed the pericardium filled with blood and a ragged rent through a contused area in the right ventricle.

If the electrocardiogram of one of these patients reveals evidence of myocardial damage, the patient should be treated as one with a myocardial infarction, with an adequate period of strict bed rest, and oxygen as long as there is any dyspnoea or tachycardia.

Penetrating Wounds of the Heart

Even in civilian practice penetrating wounds of the heart are encountered, either occasionally or frequently depending upon the locale. Many of these patients live to reach the hospital because of the sleeve-valve action of the heart beating within the pericardium which keeps the pericardial and myocardial wounds from being superimposed. This prevents exsanguination but, since the pericardium is a relatively inelastic structure and does not distend promptly, a tamponade effect is produced which prevents satisfactory filling of the heart.

The altered physical signs which result from this tamponade are rather striking. There is venous back pressure which can be observed in the distention of the neck veins, and a dusky cyanosis is usually present. The pulse pressure is markedly narrowed to about 10 mm. of mercury even before the blood pressure falls to shock levels. The heart sounds are distant or inaudible, but the rate usually is not so fast as one would anticipate for the degree of shock present.

The diagnosis can best be made with certainty by fluoroscopic observation of the lack of apparent cardiac movement. Conventional x-ray films will be of little use since the inelastic pericardium will not be immediately distended.

The Resident Staff at each of our hospitals is instructed in the emergency treatment of heart wounds. They are alerted to the fact that a penetrating instrument can reach the heart from any part of the chest wall or even the upper abdomen. Immediately on seeing a patient suspected of having such a wound, five steps are to be taken:

1) Nasal oxygen is applied immediately,
2) Plasma or whole blood is started at once with the patient in a semi-Fowler position,
3) The operating room is notified to prepare for surgery,
4) The attending surgeon is telephoned, and
5) The patient is carried to the fluoroscopic room to determine whether or not any cardiac pulsation is visible.

If the patient's condition is desperate and the diagnosis of cardiac tamponade is reasonably certain, blood is aspirated from the pericardium to relieve pressure until surgical intervention is possible. Not infrequently the wound in the myocardium has been temporarily sealed by the tamponade so that no further bleeding immediately ensues and the patient's condition improves to such an extent that one is tempted to defer exploration. Ice pick wounds

of the heart may heal permanently following one or two aspirations of the pericardium, but not so with knife wounds. Ice pick wounds of the heart may be watched closely for a few hours if the patient's condition appears to be good, but knife wounds should all be explored immediately.

A few technical points leading to improved surgical results might well be mentioned. The type of incision matters little providing that it gives adequate exposure. Future stability of the chest wall is enhanced if the sectioned ribs and cartilages are turned back as a flap and replaced when the heart repair has been effected. It is of prime importance *never* to drain the pericardium *externally*. The negative intrathoracic pressure will draw serum and skin bacteria into the pericardium and produce pyopericarditis, as we have learned from bitter experience. It is important to drain the pericardium into the pleural cavity, where bloody serum can be readily aspirated. This will avoid a collection of serum in the pericardium which would reproduce the tamponade. The choice of suture material is apparently unimportant, but care should be used to avoid where possible inclusion of any of the larger branches of the coronary arteries in the stitches. At least two of the five patients shown were subsequently accepted by the Army for military duty (Fig. 9).

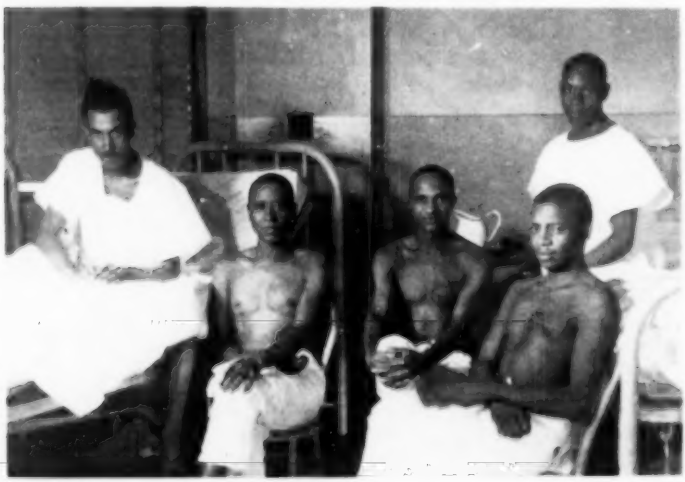


FIGURE 9: These five men were all admitted to the John Gaston Hospital in Memphis during the same two week period. Each one had a bullet or knife wound of the heart which was successfully repaired surgically and all made uneventful recoveries.

General Considerations

Relief of pain is a problem in dealing with thoracic injuries. Our objective is to relieve pain adequately without suppressing ciliary action in the bronchi or depressing the cough reflex. Pneumonitis and atelectasis being the most feared complications, opiates are used sparingly.

Pain due to fractures of ribs can most advantageously be relieved by procaine injections of the affected intercostal nerves. A single injection of each affected intercostal nerve may be sufficient to give the patient relief for several days. Ordinarily one or two such multiple intercostal nerve blocks is all that is required to relieve the majority of the patient's pain. He will then cough and raise his bronchial secretions adequately to prevent pulmonary complications.

A technical consideration in the use of intercostal nerve block is that of finding the exact level of the intercostal nerve. This is rather easily done by contacting the rib with the needle point and slipping off the lower border of the rib, advancing the needle one eighth of an inch deeper. This maneuver will avoid puncturing the lung and adding a traumatic pneumothorax to the patient's other difficulties.

The application of adhesive strapping for simple rib fractures is optional. The ribs will heal under any circumstances, and the pain from the fractures, especially if the intercostal nerves have been blocked, is at most intermittent, whereas the discomfort from the tape may be continuous. When tape is used it is advisable to paint the skin with tincture of benzoin compound. The use of Elastoplast or a similar elastic tape is also of great advantage.

The use of tape to stabilize a chest wall which exhibits paradoxical motion (flail chest) is mandatory. However, its indication is for the stabilization of the chest wall rather than for the relief of pain.

X-ray films are invaluable in treating the patient with a traumatized chest. The badly injured patient, far from being too ill to have an x-ray made, is faced with too many serious complications *not* to have one made. And as has been pointed out before, the absence of air or fluid in the pleural cavity immediately following an accident is no indication that the lung is uninjured. An appreciable and embarrassing amount of hemopneumothorax may develop several hours following the patient's injury, not detectable within the first two or three hours. Accordingly, it is good practice to repeat the initial x-ray inspection the following day, at which time it is ordinarily possible to obtain a film in the upright position, and supplement the standard posteroanterior

view with a lateral projection. This practice facilitates the removal of fluid, aids in the recognition of diaphragmatic hernias, and helps localize areas of atelectasis.

Oxygen is often required for these traumatic chest patients and the nasal catheter is strongly recommended. Its use facilitates the care of the patient, and at five to seven liters per minute flow, the patient actually obtains a better concentration of oxygen in this fashion than in the average oxygen tent. It is also more economical. Few hospital attendants understand the use of an oxygen tent. It is rare, for instance, to see a flush valve used, although this should be done for a few minutes each time the tent is opened because it requires about 30 minutes to build up the maximum oxygen concentration within a tent at the standard rate of flow, and at this rate carbon dioxide is accumulated, making the patient's respiratory efforts more violent than need be. To be effective, oxygen should be run into a tent at the rate of eight to 12 liters per minute.

Hemothorax may safely be left in the pleural cavity for the first 24 hours provided the patient's breathing is comfortable and there is no shift of the heart or the mediastinum. During this period a lung laceration will usually seal itself and bleeding from the lung will cease. However, respiratory embarrassment must be immediately relieved by aspiration. Persistent bleeding will almost invariably be found to originate from a lacerated intercostal artery or vein, an internal mammary artery, the azygos vein, or from the great vessels of the hilum of the lung. It is important, therefore, that surgical intervention with ligation of the bleeding vessel be performed in the face of persistent gross internal hemorrhage.

SUMMARY

Current practices in the treatment of chest injuries encountered in civilian practice are discussed with some consideration given their physiologic rationale.

Penetrating injuries of the chest wall and lungs, with and without sucking wounds, are discussed in some detail in regard to their emergency treatment and follow-up care.

Crushing injuries to the chest wall, with and without paradoxical motion, are described, together with their potential complications and management.

Detection and treatment of the contused heart, and the heart with a penetrating wound are described.

General consideration of complicating pneumonia, atelectasis, ileus, diaphragmatic hernia, hemothorax and other complications is given.

Recommendations are made in regard to the use of intercostal

nerve block for the relief of pain, methods of oxygen administration, and the use of x-ray assistance in the management of all types of chest injuries.

RESUMEN

La práctica habitual en el tratamiento de las heridas de tórax encontradas en la práctica civil se discute con alguna consideración a su justificación fisiológica racional.

Las heridas penetrantes de pared del tórax y pulmón con o sin traumatopnea se discuten con detalle respecto de su tratamiento de emergencia y cuidado ulterior.

Las heridas por compresión del tórax con y sin movimiento paradógico se describen así como sus complicaciones posibles y su tratamiento.

El diagnóstico y el tratamiento del corazón continudido se describen así como el de las heridas penetrantes de corazón.

Se hacen consideraciones generales sobre la neumonía secundaria, la atelectasis, ileo, hernia diafragmática, hemotórax y otras complicaciones.

Se hacen recomendaciones acerca del bloqueo de los nervios intercostales para aliviar el dolor, sobre la administración de oxígeno y el uso de los rayos X para el tratamiento de todos los casos de heridas de tórax.

REFERENCES

Altemeier, W. A. and Wadsworth, G. H.: "Ileus Following Fractured Ribs," *Annals of Surgery*, 115:32, 1942.

Betts, R. H.: "Thoraco-abdominal Injuries," *Annals of Surgery*, 122:793, 1945.

Blades, Brian: "Emergencies of Injuries of the Chest," *Journal of the American Medical Association*, 135:812, 1947.

Brewer, L. A., Burbank, B. and Samson, P. C.: "The 'Wet Lung' in War Casualties," *Annals of Surgery*, 123:343, 1946.

Burke, John and Jacobs, T. T.: "Penetrating Wounds of the Chest," *Annals of Surgery*, 123:363, 1946.

Carr, Duane: "Treatment of Injuries of the Chest," *Journal of the Tennessee State Medical Association*, 33:438, 1940.

Harmon, P. H., Baker, D. R. and Kornegay, R. D.: "Uncomplicated Fractures of Ribs and Major Injuries of the Chest Wall," *Journal of the American Medical Association*, 118:30, 1942.

Miscall, Lawrence and Harrison, A. W.: "Thoracic Surgery in a Hospital Center," *Annals of Surgery*, 125:311, 1947.

Samson, P. C., Burbank, B. and Brewer, L. A.: "Immediate Care of the Wounded Thorax," *Journal of the American Medical Association*, 129: 606, 1945.

Whitaker, L. S.: "Management of Traumatic Hemothorax," *Journal of the Tennessee State Medical Association*, 43, 1947.

The Procedures Which Make Possible the Adjustment to the Cure of the Patient With Pulmonary Tuberculosis and the Technique for Carrying Out These Procedures*

EDWARD W. HAYES, M.D., F.C.C.P., F.A.C.P.
Monrovia, California

This subject is a phase of tuberculosis work which has not received the consideration it should. It is a phase to which those engaged in research have devoted relatively little or no attention. There is no part of tuberculosis work in which there is a greater diversity of opinion and action. This great divergence perhaps accounts for this subject not being too popular for general discussion or consideration. Yet it particularly envolves the crux of all our efforts in this field, that is, the prevention of death or chronic invalidism from pulmonary tuberculosis—a disease now acknowledged as curable.

As we briefly review the history of tuberculosis control we become aware of the fact that the countless measures tried both in the prevention and the treatment of this disease down through the centuries have up to the past two or three decades been found wanting. We also find that there is still no specific for the control of this disease.

The use of BCG as a preventive measure must still be conceded in the experimental stage. The antibiotic drugs, while promising, are only adjuncts in treatment to be used always with a clear understanding of their indications and counter indications and only as an aid to the usual accepted measures of treatment. When administered otherwise their use may be harmful.

In reviewing more recent history we also find that during the past 50 years tuberculosis as a cause of death has dropped from first to seventh or eighth place. In practice this statement, or these figures, do not mean all that might be implied. Pulmonary tuberculosis continues to present the most important medical, public health, social and economic problem throughout this country, that is presented by any chronic preventable disease. It is still the first cause of death in that important age period from 15 to 35 years—the formative and productive period of life. It is estimated that there are at least 500,000 open cases of tuberculosis

*Presidential Address, Annual Meeting of the California Tuberculosis and Health Association, March 31, 1950.

in the United States—one half of which as yet have not been found. This vast army of patients continues to sow the seeds of new disease—a disease that strikes its greatest blow in the prime of life. We must not be lulled into a state of complacency by accomplishments of the past. We must face the situation as it presents itself now.

Fortunately there is a bright side to this somewhat gloomy picture. Science and clinical experience have, especially during the past two or three decades, placed at our command the measures essential for the control of tuberculosis. Today, continuous spread of this disease is unwarranted and death or chronic invalidism from tuberculosis is unnecessary. They are the result of failure to use the measures at hand. There are a few districts in this country where these preventive measures have been put into effective operation with the result that, for practical purposes, tuberculosis has been eradicated in these areas. In a group of counties in Southern Minnesota there are approximately three hundred small town and rural elementary schools where there is not a child that has been infected with the tubercle bacillus. It is true that circumstances differ in different localities. The underlying principal, however, is the same. The results obtained in any area will depend on the type and intensity of the effort made.

It is also a consoling thought, particularly to those engaged in this work, that of the nine leading or first causes of death, tuberculosis is the only one that we possess the means to eradicate.

Fundamentally, control of tuberculosis today is education. Education of the public to prevent it and education of the patient and those near and dear to him to cure it. The medical profession, that is, the profession as a whole is primarily responsible for this education. All our national organizations concerned with the control of tuberculosis now realize that the opportunity for all physicians to obtain a practical working knowledge of tuberculosis while they are medical students has been one of the most overlooked, and at the same time, the most important factor in tuberculosis control. As part of any effective tuberculosis program, the general practitioner or family physician, because of his close association with the family, must be able to occupy an important place not only in the prevention of tuberculosis but also in the treatment during what are ordinarily termed the pre- and post-sanatorium periods. The application of the principals of treatment during the active stage of the disease, or during that stage which is ordinarily called the sanatorium period, is however, a highly specialized field necessitating extensive training and experience.

In the guidance of the patient with active pulmonary tuberculosis back to health there are some four or five educational factors,

paramount in the adjustment of the patient to the cure, which he and those near and dear to him should clearly understand at the onset. That is, before the patient enters the sanatorium or begins the cure.

at the onset. That is, before the patient enters the sanatorium or begins the cure.

These factors are:

1) Pulmonary tuberculosis, regardless of the extent of involvement apparent in the lungs always seriously endangers the life of the patient unless and until it is brought under control. On the other hand it should be clearly understood by all concerned that if the patient has the right advice and guidance and the ability to take the cure he has an opportunity to regain his health and to live as long and as useful a life as he would have lived if he had not had tuberculosis. For the mental rehabilitation of the patient it is important for him to understand the possibilities of the disease. This is so closely entwined with the treatment or physical rehabilitation that it should also be begun at the outset. The two must be carried along together throughout the course of the disease. If this procedure is followed when the disease is overcome the rehabilitation is complete.

2) The treatment of pulmonary tuberculosis does not consist of the administration of medicines or drugs, it is rather an agreement or contract between the patient and those near to or responsible for the patient, and the physician. The purpose of this agreement or contract is to devise and carry out a mode of life for each patient that will enable him to regain his health. In this contract it must be understood that the patient takes the cure, the physician provides the means by education—instruction and guidance, while those near to him occupy a position of determining influence, for good or bad, depending upon whether they work with the doctor and for the adjustment of the patient or against the doctor and for the disturbance of the patient. The outcome in any case is determined for the most part by the efficiency with which each party to this agreement discharges his responsibility.

3) A certain proportion of patients, estimated to be about one out of every four, who have pulmonary tuberculosis, even though the disease may be in the advanced stages, will overcome their disease and regain their health without treatment, or in spite of treatment, providing the treatment which may have been instituted does not interfere with the normal course of their disease. Patients in this category are those who develop what is classified as the resolving type of pulmonary tuberculosis—a type of the disease which is not influenced by treatment. The reasons why some patients develop this type of disease is not entirely under-

stood. They are usually explained on the basis of the size and severity of the infection and the degree of the allergic response to the infection. It is patients with this type of disease who are responsible for the popularizing of unorthodox or special types of treatment or treatment by quack remedies and nostrums. The other three patients out of the four, in attempting to overcome their disease, as these patients were able to do, will lose their lives of a disease that is curable. At the onset there are no means by which it can be determined in which patients the disease will clear up if treatment is not instituted. All patients must take the cure and be guided with the utmost caution until it is clearly evident what course their disease will follow.

4) There are no two patients in which pulmonary tuberculosis develops in the same way. Likewise there are no two patients who respond in the same way to the cure. This is true because there are no two patients who have the same resistance to the tubercle bacillus and the products of its growth and destruction; there are no two patients who are infected with the same dosage of tubercle bacilli or with bacilli of the same virulence; there are no two persons who are able to adjust themselves to the cure in the same way and there are many other variables that enter into the comparison of any two patients. Consequently, while there are a few general principles that apply to the care of all patients with tuberculosis, the details of treatment must be worked out for each patient according to the indications in his particular case. It is attention to details that cures tuberculosis. It is failure to pay attention to details that causes most patients who lose their lives with tuberculosis, to die. The institution of and the carrying out of the details essential for the individual patient is made possible only by a close patient-physician relationship—a relationship attainable only through a mutual understanding and a mutual confidence.

5) Tuberculosis is not cured by climate or diet or drugs or by exposure to the sun's rays. Experience has demonstrated that when the treatment which patients receive is relatively the same, the results obtained in the different climates are relatively equal. There is no special diet to be used in the treatment of pulmonary tuberculosis. Patients with this disease require a balanced nutritious diet. They should not be over-fed. The digestive system needs rest as does the body as a whole. The diet should be regulated so that patients underweight gain at the rate of three or four pounds a month up to normal or a little above normal and the diet should then be adjusted to hold that weight. The type and quality of the food and the manner in which it is served should be such as to tempt the appetite. It is best that the food be served in three fairly

equal meals a day, avoiding between meal feeding, except in special cases, as it tends to interfere with the appetite for the regular meals. It should be made clear to the patient that he must eat to overcome his disease; that eating is a habit; that not eating is a habit and that appetite comes with eating. The patient's attitude toward his food and his ability to take it and digest it are the determining factors as to whether or not he is able to eat and digest his food.

Drugs or medicines, other than the antibiotics, if and when employed in the treatment of pulmonary tuberculosis, are used to treat symptoms and complications. Patients adjusted to the cure, regardless of the stage of their disease, rarely have symptoms or complications. When patients on treatment have symptoms they are usually functional rather than organic. They are the result of the physiology of the body being disturbed by the emotions. These symptoms are real—not imaginary. It is well, as it is effective, to explain to patients that most symptoms which occur in people, in general, are not due to organic disease as our physiologists point out, but are rather the result of a disturbance in their physiological equation. It should be explained to the patient how the endocrine glands control the physiology of the body. Have them understand that when people are calm and relaxed they are so because these particular glands are then secreting just enough of potent drugs as histimine, epinephrine, ephedrine, thyrotoxin and others to maintain the physiological reactions at a normal level. It should be understood that the endocrine glands are susceptible to the emotions and when patients are emotionally upset by worry, anxiety or even joy an excess of these drugs is released into the system. As a result there occur various symptoms or combinations of symptoms such as insomnia, anorexia, indigestion, excessive cough, rapid heart action and weakness. The treatment of these symptoms is not the administration of drugs which will further upset their physiology. These patients should be given the vocal sedative, that is, they must be talked to so that they will understand and be reassured and relaxed. The treatment of pulmonary hemorrhage occurring in connection with pulmonary tuberculosis with narcotics or sedatives which interfere with or destroy the cough reflex is an illustration of the possible deleterious effect resulting from the disturbance of the normal physiology by the use of these drugs. The usual result of this method of treating pulmonary hemorrhage is retention of the aspirated blood—atelectasis—and dissemination of the tuberculosis. The treatment of pulmonary hemorrhage is again the vocal sedative through reassurance.

Sitting in the sun's rays, especially in the heat of the day, is

mentioned only to be condemned as a hazardous procedure for patients with active pulmonary tuberculosis.

In brief the treatment of pulmonary tuberculosis is the management of the individual; the management from every angle, especially the psychological. More specifically it is the outlining of a mode of life for each patient according to the indications in his case and the control of the patient so that he follows that mode of life according to strict detail. The basis for this mode of life is rest and time—rest carried out over a sufficient length of time to accomplish the desired results. Physiologists regard rest as the natural defense of the body. Cannon, the renowned physiologist, in discussing rest remarked that every physician knows that given rest (rest for the body), and peace of mind (rest for the mind), and proper food, 90 per cent of his patients will get well. Allen Krause writing about rest in the treatment of tuberculosis in 1918 said that until every patient on being asked, "what is the most important factor in the treatment of tuberculosis," will unhesitatingly answer, "rest," the discussion of the subject will always be timely.

What is rest for a patient with pulmonary tuberculosis? Rest for a patient with pulmonary tuberculosis is not synonymous with the term rest for a tired healthy person. Rest in the treatment of tuberculosis must be more than a lip service. While the quantity and duration of the rest is important, the basic emphasis must be placed on the quality of the rest. Rest for a patient with tuberculosis means lying in the horizontal position, mentally and emotionally relaxed, 24 hours a day, seven days a week and 52 weeks a year, for as many months or years as may be necessary for any particular patient to control his disease. Patients should know that it is possible to undo in five or 10 minutes what they have accomplished in months by injudicious activity. Patients should be instructed to lie for the most part in that position in which they will be most comfortable. When patients are in the semi-reclining position or are sitting up, the vertical excursion of the lungs during respiration ordinarily is not as great as it is in the horizontal position but, when they are permitted to assume these positions, patients as a rule, interpret this permission as a license to indulge in various other oftentimes harmful activities. Patients should be told to turn on either side for 10 or 15 minutes, using as little energy as possible, every three or four hours during the periods they are awake, so as to promote pulmonary drainage. Frequently cavities or the major portion of the disease are located toward the posterior part of the lung and this maneuver will tend to decrease useless cough and relieve toxemia by facilitating drainage of these areas. The duration and degree of intensive rest will

be determined in most part by the extent and acuteness of the disease, the physician's control of the patient and the ability of the patient to adjust himself to the cure. At the beginning of the treatment all patients should be placed on a strict rest regimen. This affords the patient an opportunity to think and realize that he has a serious task on hand; it enables him to realize that this task can be accomplished only by self control and self discipline; it also affords the physician an opportunity to study, to observe and to evaluate the patient and his condition under circumstances where the patient will do himself the least harm.

Persons on the cure for active pulmonary tuberculosis must be taught and trained to follow a strict regimen. Any permitted deviation, especially at the outset, tends to lead to other deviations.

Mental and emotional relaxation is imperative. Without this it is not possible to rest physically. As Pinner pointed out, being in bed is not bed rest for a patient with pulmonary tuberculosis. When these persons are not controlled mentally, emotionally and physically they will consume needless energy and at the same time interfere with the delicate healing process in the lungs and flood their systems with toxins from the pulmonary foci by fretting and fussing and worrying, by twisting and turning, by popping up in bed and by reaching for this and for that, by lying in strained positions, by pulling at the bedding, and by excesses in talking and being talked to, in reading, in writing, in listening to the radio and in countless other needless activities. Any activity—mental, emotional or physical—increases activity in the lungs and of the lungs. The objective is to reduce lung activity to a minimum. The more nearly patients with pulmonary tuberculosis approach the state of vegetating the more gratifying the results.

Mental and emotional rest for the patient with pulmonary tuberculosis is secured by treating him as an individual and by placing him in an environment that will make his adjustment possible. The primary factor in treating the patient is to tell him the truth. It is the uncertainties or the unknown in life that upset persons, regardless of what walk of life is involved. The truth may be and often is a great shock at the outset, but in practice it is only by knowing and understanding the truth that patients are able to adjust themselves to the situation and to meet it with intelligence and efficiency.

When the diagnosis of pulmonary tuberculosis is established, the physician must take time—usually from one to two hours or longer to talk to the patient and those near to him. He should have the opportunity to tell them about tuberculosis and about the patient's tuberculosis. He should show them the x-ray pictures of the patient's chest and compare these pictures with those of

a normal chest, and with any previous ones of the patient's chest that may be available. It always has a marked influence in promoting the adjustment of the patient to the treatment to show him the serial x-ray pictures of the lungs of other patients who have had as much or more involvement than he has and who have regained their health by strict adherence to the cure. At the same time it is well to show him the serial pictures of patients who had less pulmonary involvement than he has and who have failed to regain their health because they ignored the details of the cure.

In spite of the difficulties that arise in the interpretation of x-ray pictures of the chest, the explanation of the patients pictures to him has a marked, as well as a gratifying influence in enabling him to visualize his disease and to adjust himself to the cure. The patient, and those near to him, must be told about the cure. They should understand what is meant by the cure and the part the patient and those responsible for him must play. They must understand what and what not to expect from the doctor. They should always understand that it is the patient's tuberculosis, that it is his life that is at stake, that it is he who must take the cure; that during this period he has just one business and that is to get well, and that there are no short cuts to recovery.

There is nothing that will save the physician's time more than the preparation of the patient and those on whom he depends for the task ahead, by a painstaking explanation of the situation as a whole before the patient begins the cure. With this approach, and with the advantage of the right atmosphere, it is rare after the patient begins the cure, even when the course of his disease is one of years, that it is necessary for the physician to spend more than a moment or two with him as he makes his observation rounds. What has been said throughout this discussion applies with equal emphasis to patients of all types and to those cared for under public or private circumstances.

A sanatorium must not be regarded as just a place where the individual has a bed and a tray and a nurse and a physician. A sanatorium, if it serves its purpose, is in the first place an atmosphere where each patient is taking the cure as he should for his tuberculosis. Consequently, each patient has the moral support and mutual sympathy of all the other patients as well as the beneficial influence of mass psychology. These factors exert a powerful influence in enabling patients to adjust themselves to the cure. In the second place, a sanatorium must be an educational institution where the patient is taught and trained how to get and stay well.

Many and varied "reasons" are presented for patients leaving

sanatoria against medical advice. Most of these reasons are in reality only excuses advanced by the maladjusted patient. There are three fundamental reasons why they leave the sanatorium contrary to physician's advice, as follow:

1) Failure of the physician to sell the cure and himself to the patient and to those responsible for him at the outset.

2) Failure of the sanatorium to perform its function as an atmosphere conducive to the patient's adjustment to the cure.

3) Occasionally there is a patient who has an uncontrollable psychological imbalance independent of his tuberculosis.

In other words when the patient has been skillfully approached by the physician, before he enters the sanatorium, and has had his disease and the cure explained to him he enters upon his task with a determination to recover, that is, the patient in turn sells himself the cure. The patient's ability to sell it to himself will depend for the most part upon the influence which his physician has over him and upon his environment.

The degree to which any patient has controlled his disease is determined largely by the reaction of his condition to graduated exertion. The physician must be the judge as to when this may be prescribed. Such exertion is carefully increased and carried out in a systematic course under close supervision which enables the physician to observe the reactions and to guide the patient to a physical and mental state of rehabilitation.

Mechanical and antibiotic therapy should be considered in the care of all patients on the cure for pulmonary tuberculosis. At the beginning, however, unless there are definite indications to the contrary, all should have an opportunity for a period of time—usually from three to six months—to demonstrate whether or not they can control their disease on the rest regimen alone.

Peck feels that we, for the most part, turn our backs on rest by giving it lip service only. He feels that in most sanatoria today collapse or mechanical therapy is instituted so early in treatment that there is no opportunity for the physician to determine what rest alone will accomplish. Pinner expressed the opinion that the physician's estimation of the value of rest in the treatment of pulmonary tuberculosis is entirely dependent upon his willingness to try rest over a sufficient length of time and under circumstances that will enable him to have a knowledge and understanding of what rest will accomplish.

Mechanical treatment of pulmonary tuberculosis is now developed to a high degree of efficiency. Today, when judiciously employed, it is instrumental in saving the lives of a vast number of patients with pulmonary tuberculosis and restoring them to a social and economic state of efficiency. The antibiotics when used

as indicated are likewise instrumental in enabling many patients with tuberculosis to regain their health.

Mechanical and antibiotic therapy, however, are not the treatment of pulmonary tuberculosis. Rest is the treatment. Mechanical therapy and the antibiotic drugs supplement rest but they do not supplant it.

REFERENCES

Krause, Allen K.: An Editorial, Reprinted from the *American Review of Tuberculosis*, 1:680, 1918.

Pinner, Max: "Pulmonary Tuberculosis in the Adult." *Charles C. Thomas Co.*, Springfield, Illinois.

Peck, William M.: "The Modalities of Bed Rest." *Public Health Reports*, Vol. 61, No. 18, May 3, 1946.

Control of Vestibular Toxic Effects of Streptomycin by Dramamine*

L. L. TITCHE, M.D.† and ANDREW NADY, M.D.††
Tucson, Arizona

From the beginning of its use in the treatment of pulmonary tuberculosis, the toxic effects of streptomycin on the vestibular apparatus has been noted.[3,9,12,16] These actions varied from complete and irreversible loss of vestibular function in the majority of patients treated[4,6-8,15,24] to symptoms of vestibular dysfunction with a return to normal after the cessation of therapy.[9,16]

The site of the lesion in the vestibular apparatus was believed by some investigators to be in the peripheral portion[9,14,25] and by others to be central,[19,26] while Snell[18] and Moffitt and Norman[17] found features of involvement of both. Bunn[4] believes that the labyrinth died completely and Dix[7] concluded that streptomycin had a selective toxic action upon the vestibular apparatus.

After streptomycin had been used on quite a number of cases, it was discovered that a reduction in the total amount of drug administered brought about a decrease in the number of patients who showed vestibular involvement.[2,21-23] At first it was believed that the eosinophilia and histamine-like reactions observed were due to impurities in the drug,[12] since the large number of patients showing this, decreased following a reduction in total dosage. Bignall and Crafton[1] found that benadryl (Beta-dimethyl-aminoethyl benzhydryl ether hydrochloride) abolished or considerably reduced nausea and vomiting, and Fowler and Feind[10] reported that cats given neo-antergan (N-p-methoxybenzyl N',N'-dimethyl-N - a - pyridylethylene - diamine maleate) or pyribenzamine (N,N-dimethyl-N'-benzyl-N'- [a-pyridyl] -ethylenediamine monohydrochloride) along with streptomycin, showed prolongation of the time before otic symptoms developed.

In 1949, Guy and Carliner[11] reported the effectiveness of dramamine (B-dimethylaminoethyl-benzohydryl ether 8-chlorotheophyllinate) in the prevention or reduction of seasickness. This was

*Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Chief, Eye, Ear, Nose and Thorat Section, Veterans Administration Hospital, Tucson, Arizona.

††Chief, Tuberculosis Section, Veterans Administration Hospital, Tucson, Arizona.

followed by the work of Strickland and Hahn[20] with this drug in decreasing the incidence of airsickness. Campbell[5] observed a reduction of symptoms of vestibular reactions in patients following the labyrinthine fenestration operation when this drug was employed.

For the past several years, streptomycin has been employed in the treatment of tuberculosis at this hospital. Many patients, while receiving this substance, complained at various times of a feeling of "light-headedness" or of dizziness. No dysfunction of the vestibular apparatus could be demonstrated in these cases either before or after the appearance of these symptoms. After the reports of the use of dramamine for the relief of these symptoms, but due to other causes, it was felt that this drug possibly could give symptomatic relief to these patients.

A detailed study was made on nine patients. All of them received streptomycin in doses of 1 gm. a day except one, a case of tuberculous meningitis, who received 150 gms. in 38 days and 0.85 gms. intrathecally. The onset of dizziness varied from 12 to 49 days after the beginning of administration of the drug, with an average of 28.7 days. The patient with tuberculous meningitis had his onset of severe dizziness 32 days after therapy was begun. The dizziness varied from mild "light-headedness" to such severity that the patient was very conscious of it.

None of the patients complained of tinnitus or any disturbance of hearing. Audiometric and caloric tests revealed no significant deviation from the ones performed before the beginning of streptomycin therapy. The patients were given dramamine in doses from 150 to 400 mgm. daily for from one to 28 days, with an average of 5.3 days. Symptoms disappeared in from one to seven days, with an average of 3.57 days except in two patients who still had dizziness after 28 and 90 days of dramamine, the latter being the case of tuberculous meningitis.

Bearing in mind the possibility that the symptoms could be due to an allergic reaction to streptomycin, a determination of the eosinophils in the blood was made before dramamine was given and after it had been discontinued. The number of eosinophils at the onset of symptoms varied from two to 10 with an average of five. After cessation of therapy, the eosinophil count was from one to four with an average of four. We believe that this demonstrates that an allergic reaction did not occur.

SUMMARY

From the above, it is our opinion that dramamine is a useful drug in the symptomatic relief of the dizziness which is encountered during streptomycin therapy. Further investigation may

reveal that this drug may prevent the toxic effects of streptomycin on the vestibular apparatus.

RESUMEN

De acuerdo a lo dicho mas arriba, nosotros opinamos que la dramamina, es una droga útil en el tratamiento sintomático del vértigo, que se encuentra durante el tratamiento con la estreptomicina. Mas investigación en la materia, tal vez demuestre que esta droga puede prevenir los efectos tóxicos de la estreptomicina, en el aparato vestibular.

REFERENCES

1 Bignall, J. R. and Crafton, J.: "Antihistamine Drugs in Treatment of Nausea and Vomiting Due to Streptomycin," *Brit. M. J.*, 4591:13, 1949.

2 Bogen, Emil: "Streptomycin Dosage in the Treatment of Tuberculosis," *Dis. of Chest*, 16:761, 1949.

3 Brown, H. A. and Hinshaw, H. C.: "Toxic Reaction to Streptomycin on the Eighth Nerve Apparatus," *Prof. Staff Meet., Mayo Clin.*, 21:347, 1946.

4 Bunn, Paul A.: "Streptomycin in the Treatment of Human Tuberculosis," *Dis. of Chest*, 14:670, 1948.

5 Campbell, E. H.: "The Effectiveness of Dramamine in Relieving the Vestibular Reactions Following the Labyrinthine Fenestration Operation," *Laryngoscope*, 59:1261, 1949.

6 Chase, J. S.: "Toxic Effects of Streptomycin on the Eighth Nerve," *Am. Rev. Tuberc.*, 56:418, 1947.

7 Dix, M. R.: "The Effects of Streptomycin on the Eighth Nerve System," *J. Laryng. and Otol.*, 62:735, 1948.

8 Domon, C. M., Kilbourne, P. C. and King, E. Q.: "A Clinical Study of the Toxic Effects of Dihydrostreptomycin and Streptomycin," *Am. Rev. Tuberc.*, 60:564, 1949.

9 Farrington, R. F., Hull-Smith, H., Bunn, P. A. and McDermott, W.: "Streptomycin and Toxicity: Reactions to Highly Purified Drug on Long-Continued Administration to Human Subjects," *J.A.M.A.*, 134: 679, 1947.

10 Fowler, E. P. Jr. and Feind, C. A.: "Toxicity of Streptomycin for the Auditory and Vestibular Mechanisms," *Am. Rev. Tuberc.*, 60:39, 1949.

11 Gay, L. N. and Carliner, P. E.: "The Prevention and Treatment of Motion Sickness: I. Seasickness," *Science*, 109:359, 1949.

12 Hinshaw, H. C., Feldman, W. H. and Pfuetze, K. H.: "Streptomycin in Treatment of Clinical Tuberculosis," *Am. Rev. Tuberc.*, 54:191, 1946.

13 Moffitt, P. O. Jr. and Norman, W. B.: "Streptomycin Toxicity to the Labyrinth," *Ann. Otol., Rhinol. and Laryng.*, 57:999, 1948.

14 Mushett, C. W. and Mortland, H. S.: "Pathologic Changes Resulting from Administration of Streptomycin," *Arch. Path.*, 42:619, 1946.

15 Peik, D. J., Hogh, H. Jr. and Campbell, P. A.: "Streptomycin Toxicity of the Eighth Nerve," *Arch. Otolaryng.*, 50:251, 1949.

16 Pfuetze, K. H., Glover, R. P., White, E. F. Jr., Feldman, W. H. and Hinshaw, H. C.: "Clinical Use of Streptomycin in the Treatment of Tuberculosis," *Dis. of Chest*, 12:515, 1946.

17 Pfuetze, K. H. and Ashe, W. M.: "Present Status of Streptomycin in Tuberculosis," *Dis. of Chest*, 14:446, 1948.

18 Snell, F. B.: "Some Otic Complications of Streptomycin Therapy," *Mil. Surgeon*, 102:202, 1948.

19 Stevenson, L. D., Alvord, E. C. Jr. and Correll, J. W.: "Degeneration and Necrosis of Neurones in Eighth Cranial Nuclei Caused by Streptomycin," *Proc. Soc. Exper. Biol. and Med.*, 65:86, 1947.

20 Strickland, B. A. and Hahn, G. I.: "The Effectiveness of Dramamine in the Prevention of Airsickness," *Science*, 109:359, 1949.

21 Tompsett, Ralph: "Relation of Dosage to Streptomycin Toxicity," *Ann. Otol., Rhinol. and Laryng.*, 57:181, 1948.

22 Tucker, William B.: "Factors Influencing the Outcome of Streptomycin Therapy in Pulmonary Tuberculosis," *Dis. of Chest*, 16:714, 1949.

23 Tucker, William B.: "Evaluation of Streptomycin Regimens in the Treatment of Tuberculosis," *Am. Rev. Tuberc.*, 60:715, 1949.

24 Wallner, L. J.: "The Otologic Effects of Streptomycin Therapy," *Arch. Otolaryng.*, 49:108, 1949.

25 Winston, Julius: "Vestibular Findings Before, During, and After Vestibular Damage Resulting from Streptomycin Therapy," *Arch. Otolaryng.*, 47:746, 1948.

26 Winston, J., Lewey, F. H., Parenteau, A., Marden, P. A. and Cramer, F. B.: "An Experimental Study of the Toxic Effects of Streptomycin on the Vestibular Apparatus of the Cat," *Ann. Otol., Rhinol. and Laryng.*, 57:738, 1948.

FIRST INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Five hundred physicians from 43 countries assembled in Rome to attend the First International Congress on Diseases of the Chest at the Carlo Forlanini Institute. Dr. Louis Mark, President of the American College of Chest Physicians, made the opening address. Dr. Jay Arthur Myers, Past President of the College and Chairman of the Committee on Awards, presented Sir Alexander Fleming, F.C.C.P. (Hon.), discoverer of Penicillin, with the College Medal for meritorious achievement in the specialty of diseases of the chest. A more detailed report of this important congress will appear in the next issue of the journal.

SEMI-ANNUAL MEETING, BOARD OF REGENTS

The semi-annual meeting of the Board of Regents of the College will be held at the Hotel Statler, Cleveland, Ohio, on Sunday and Monday, December 3 and 4, 1950. The scientific session will take place on December 3 and meetings of the various councils of the College and of the Board of Regents will be held on December 4. Dr. Joseph C. Placak, immediate Past President of the College will be in charge of arrangements. The Interim Session of the American Medical Association will be held in Cleveland, Ohio, December 5 through 8, 1950.

NEXT ANNUAL MEETING

The Seventeenth Annual Meeting of the American College of Chest Physicians will be held in Atlantic City, New Jersey, June 7-10, 1951. The Committee on Scientific Program for the 1951 meeting has been organized, consisting of the following members:

Edwin R. Levine, M.D., Chicago, Illinois, Chairman
Alvin L. Barach, M.D., New York, New York
Paul H. Holinger, M.D., Chicago, Illinois
Richard H. Overholt, M.D., Brookline, Massachusetts
Leo G. Rigler, M.D., Minneapolis, Minnesota
Harold G. Trimble, M.D., Oakland, California

Physicians interested in obtaining places on the scientific program are invited to submit titles and abstracts of their material to Dr. Edwin R Levine, Chairman of the Committee, 109 North Wabash Ave., Chicago, Ill

SOCIETY OF TUBERCULOSIS, ROSARIO, ARGENTINE

The Rosario Society of Tuberculosis of Argentine held its Annual Meeting an April 24, at which time the following officers were elected:

Justo Lopez Bonilla, M. D., President
Isaac Alberto Hassan, M. D., Secretary
Raul Garbulsky, M. D., Secretary, Scientific Program
Noe Dlugovitzky, M. D., Treasurer
Juan Carlos Barberis, M. D., Adviser
Rodolpho Delpino, M. D., Adviser
Raul Taltavull, M. D., Adviser

MEXICAN SOCIETY OF TUBERCULOSIS

The Mexican Society of Tuberculosis announces that the Fourth National Congress of Tuberculosis and Silicosis will take place in the city of San Luis Potosi, Mexico at the Central Hospital, January 21-27, 1951. Members of the American College of Chest Physicians have been invited to present scientific papers. For further information, write to the Central Hospital, San Luis Potosi, Mexico.

INTERNATIONAL COLLEGE OF SURGEONS

The Fifteenth Annual Assembly of the United States Chapter of the International College of Surgeons will take place at the Cleveland Auditorium, Cleveland, Ohio, October 31-November 3, 1950. For further information, write to Arnold S. Jackson, M. D., Secretary, 1516 Lake Shore Drive, Chicago 10, Illinois.

ECUADORIAN SOCIETY OF TUBERCULOSIS

The Ecuadorian Society of Tuberculosis held its Annual Meeting in Guayaquil on June 6, at which time the following officers were elected:

Euro Torres Leon, M. D., President
Eduardo Rendon, M. D., Vice-President
Aurelio Garcia Santos, M. D., Secretary
Francisco Marchan, M. D., Secretary, Scientific Program
Juan J. Villacis P., M. D., Treasurer
Mauro Madero, M. D., Librarian
Marco Martinez Macias, M. D., Adviser
Joffre Lara M., M. D., Adviser

TWO RESEARCH FELLOWSHIPS IN PEDIATRIC ALLERGY

These Fellowships will be full time. One starts July 1, the other, January 1. They carry a stipend of $2,000 per year. Applicants must be certified in Pediatrics or have the requirements for certification. The Fellowships run from one to two years and will consist of intensive training in Immunology and Animal Research pertaining to the field of hypersensitiveness; intensive study of allergic children, which will include skin testing, laboratory work, clinical follow-up, as well as clinical research. Applicants who have had previous training in Chemistry and or Immunology, and who are desirous of a research career will have preference.

Applications should be made to the Office of the Dean: New York Medical College, 106th Street and Fifth Avenue, New York, New York.

1948 TUBERCULOSIS MORTALITY RATE

The annual death rate from tuberculosis dropped 10 per cent in 1948 to 30.0 per 100,000 population, as stated in the current Tuberculosis Control Issue of *Public Health Reports*, published by the Public Health Service, Federal Security Agency.

The decline in the tuberculosis mortality rate, the article points out,

has accelerated during the post-war years. The rate dropped 5 per cent from 1945 to 1946, and 7 per cent from 1946 to 1947.

The tuberculosis death rate for the population as a whole has been steadily declining for the past twenty years, so that the 1948 rate was less than half the 1930 rate, according to the article. The decline is sharper in some sections of the population than in others—sharpest of all in children under 15 years of age. In persons over 65 years of age, on the other hand, the decline has been slow, and indeed in white males over 65 the tuberculosis death rate was higher in 1948 than in 1941.

In general, the article points out, the tuberculosis death rates for women have fallen more rapidly than those for men. The 1948 rate for females was about half of that for males. Mortality rates from this disease continue to be more than three times as high for the non-white groups as for the white, the article says.

The State with the lowest tuberculosis death rate in 1948 was Iowa with a rate of 9.5 per 100,000 population. The State with the highest rate, Arizona, dropped from 100 in 1947 to 82.4 in 1948.

Obituaries

EUGENE CYRUS HAWKS

1892 - 1949

Doctor Eugene Cyrus Hawks was born May 15, 1892. He was the son of Osborne and Olive I. Hawks. He attended the College of Liberal Arts at the University of North Carolina for two years. He transferred to the University of Virginia where he studied one more year before enrolling in the University of Maryland, School of Medicine where he graduated with the degree of Doctor of Medicine in 1921. He was licensed to practice medicine in the State of Maryland in 1921. His studies were interrupted by the First World War in which he served in the armed forces. While serving his internship at the Hazelton Sanatorium he developed pulmonary tuberculosis from which he recovered rather promptly. His illness, instead of being a handicap, seemed to enhance his interest in diseases of the chest. He worked and studied at Mount Alto Sanatorium, Mount Alto, Pennsylvania, Pine Camp Hospital, Richmond, Virginia, the Catawoba Sanatorium, Virginia, and took postgraduate work at the Johns Hopkins University, School of Medicine. He settled in Rockville, Maryland where he practiced medicine until his untimely death on December 16, 1949 of intestinal obstruction. Throughout his career in private practice he showed great interest in diseases of the chest, particularly pulmonary tuberculosis and was unusally talented with the stethescope. He became physician to Georgetown University, Sebly Memorial, Providence, Childrens, Surburban and Doctors Hospitals, Washington, D. C. and clinician to the Tuberculosis Clinic and Venereal Disease Clinic of the Montgomery County Hospital. He was a fellow of the American College of Chest Physicians and the American Medical Association and a member of the Montgomery County Medical Association. He leaves behind a host of friends and colleagues.

J. W. HUSTON

1875 - 1950

Doctor Huston was born September 20, 1875, a native of Granville, Illinois. He graduated from Knox College, with a B. S. Degree in 1899, and received his medical education at Rush Medical College, graduating in 1904.

He came to Asheville in 1910, and soon entered his long and active career of Medical Practice. He became interested in tuberculosis, and became an understanding specialist in diseases of the chest.

He was past president of the Buncombe County Medical Society; a member of N. Carolina State Medical Society, the Southern Medical Association, the American Medical Association, and a member of the American College of Chest Physicians. He was, for many years, a member of the Board of Directors and Dean of the Nurses' Training School of Biltomore Hospital, Asheville, North Carolina. He was, also, Medical Attendant to the Kiwanis Preventorium for underprivileged children, which he helped to organize. Dr. Huston was a member of the Board of Elders of the First Presbyterian Church, and was active in church work, and spent much of his time in the interest of public welfare.

Dr. Huston will be greatly missed by the profession, where he was recognized for his ability, and admired for his honesty and integrity.

GEORGE W. WALLERICH

1880 - 1950

George W. Wallerich, president of V. Mueller & Company, Chicago, Illinois, died July 3, 1950 after a long illness. Mr. Wallerich, who was born on April 3, 1880, had been an eminent leader in the surgical instrument industry for more than forty-five years. Forty years of this time were spent with the Chicago surgical instrument house which he joined as secretary shortly after his marriage to Vinzenz Mueller's daughter, Marie. Previously he was sales manager of the Victor X-Ray Corporation, during which time he was regarded as one of the country's outstanding authorities on x-ray equipment and techniques.

NEW PARASAL TABLETS SAID TO MINIMIZE SIDE EFFECTS

A new form of Parasal—para aminosalicylic acid, Panray—which tends to minimize or completely eliminate gastro-intestinal disturbances in the chemotherapy of tuberculosis has been announced by the Panray Corp., manufacturers of fine medicinal chemicals. Prepared from a highly purified, parenteral grade of sodium PAS (dihydrate), the drug is in tablet form, specially coated for uniform and complete disintegration and absorption.

Each tablet contains 0.69 gms. Parasal sodium, which gives the equivalent activity of exactly 0.5 gm. para aminosalicylic acid. Despite the increased weight, it is little larger than the regular 0.5 gm. tablet and just as easily swallowed.

Parasal Sodium tablets, 0.69 gm. are available as yet to qualified investigators only. Literature is available on request from the Panray Corp., 340 Canal Street, New York 13, New York.

DOUGLAS J. KING JOINS HEYDEN CHEMICAL CORPORATION

Heyden Chemical Corporation of New York City is happy to announce the appointment of Mr. Douglas J. King to position of Assistant to Mr. Q. S. Ball, Manager of the Professional Products Division.

Mr. King has had extensive experience in the drug and pharmaceutical industry and is well qualified for this important position in the sales and merchandising of Heyden Penicillin and Streptomycin. These well-known antibiotics are produced in Heyden's modern Princeton, N. J. plant, and enjoy an unusually widespread preference and use in the field, due to the high quality of the products themselves, and the sales and merchandising abilities of Mr. Ball and his well-trained technical organization.

THE MERCK MANUAL OF DIAGNOSIS AND THERAPY

Merck & Co., Inc., announces the publication of the eighth edition of *The Merck Manual of Diagnosis and Therapy*. This completely rewritten, Golden Anniversary edition of *The Merck Manual* fills the need for an accurate and concise reference source of information on the remarkable advances in medical sciences that have occurred during the past decade. The first edition was published in 1899, and the last preceding edition in 1940.

Approximately 1,600 pages long, with 338 chapters on diseases and major symptoms, the completely new volume is replete with up-to-date information, including current knowledge on antibiotics, the sulfonamides, and the anticoagulants, and on therapy employing adrenocortical steroids or substances of related action.

The new edition was prepared under the supervision of the Merck Medical Division, with the collaboration of leading clinicians throughout the United States.

Price will be $4.50 for regular edition and $5.00 for a thumb-index edition. Orders for copies of *The Merck Manual* should be addressed to Merck & Co., Inc., Rahway, New Jersey.

NEW PILLING STORAGE BATTERY

George P. Pilling & Son Co., of Philadelphia, one of the country's oldest and largest surgical instrument houses has just announced a new, portable, practically fool-proof storage battery unit that is both powerful and dependable. It weighs only 16 pounds and can be easily carried around by even the smallest O.R. nurse.

The unit contains two 4 volt, 6 ampere non-spill storage cells in transparent plastic cases. Only one is used at a time, leaving the second always in reserve. A rheostat allows instant regulation of the brightness of the lamps, and a quick change from one battery to the other by the flip of a switch does not require any changes of the instrument light cord tips. The condition of each battery may be determined by a glance at the charge indicator. And recharging is simple with the built-in charger. Can be plugged in the regular house current if it is the usual 110-115 volt, 60 cycle AC. Descriptive literature is available.

CORTISONE

Cortisone is now available to a large number of hospitals throughout the United States under the trade mark "Cortone," it was announced by Merck & Co., Inc., manufacturing chemists, who first produced the drug by chemical synthesis.

For a temporary period, Cortone will be supplied only to those hospitals having certain minimum facilities operated by trained technicians, and under the supervision of qualified physicians. Hospitals registered by the American Medical Association, numbering approximately 6,500 throughout the United States, meet these requirements and are qualified to receive Cortone. The Journal of the American Medical Association lists these hospitals in its May 6, 1950 issue.

As stated in the directions which accompany each vial of Cortone, the drug is to be used, during the initial period of treatment, only in patients hospitalized in these institutions. This stipulation is considered essential for the present by the Food and Drug Administration, for safe use of the product.

Cortone will be delivered to these hospitals in packages of three vials, each vial containing 300 milligrams of the substance. The price to hospitals will be $28.50 per vial, equivalent to $95.00 per gram. This is the fourth in a series of price reductions which have brought the price down from an original figure of $200.00 per gram, the amount first paid by qualified clinical investigators.

Steadily increasing production of Cortone and the accumulating knowledge concerning its use in rheumatoid arthritis and other diseases have made this limited distribution possible.

Although the complex chemical nature of this substance and the scarcity of raw materials have imposed unprecedented manufacturing difficulties, the supply of this drug is now more than sufficient to cover all the needs of clinical investigation and other research. When applied to the treatment of disease, however, present supplies and production of this compound are unfortunately far short of the total need to treat all the patients with diseases for which Cortone is recommended.

During the intervening months since the first announcement of the dramatic results obtained at the Mayo Clinic, Cortone has been under active investigation by more than a thousand medical authorities throughout the United States and Canada, as well as by a large number of research workers in the fundamental sciences. As a result of these studies, a large body of information has been accumulated on the biologic action and therapeutic uses of this medicinal agent. The drug has demonstrated dramatic effects in the control (not cure) of most rheumatic diseases, particularly those which are not too far advanced.

STOMACH X-RAYS

A new type of x-ray equipment that will permit the taking of stomach x-rays has been installed in the offices of the Du Pont Company's Medical Division in Wilmington, Delaware.

Dr. G. H. Gehrmann, medical director, said the new machine represents one of the most recent advances in diagnostic equipment, and is one of only a few such machines now in operation in the country. The original

machine was developed at The Johns Hopkins University in Baltimore, where it has been in use for some time.

Dr. Gehrmann states: "This method is not final in establishing diagnosis and further investigation is sometimes necessary. Cancer of the stomach, if diagnosed at a very early stage, can be removed by surgery with a very high chance of complete cure. It can be detected by x-ray examination before there are any significant symptoms and before the individual knows that there is anything wrong with him."

The new machine, which takes a series of six pictures with a specially designed Schmidt-type camera, was developed by Dr. Russell Morgan and Dr. John F. Roach of the Department of Radiology at Johns Hopkins for making mass surveys and was installed here under their direction. All films taken in the Du Pont medical offices will be sent to Drs. Morgan and Roach, Dr. Gehrmann said. They will interpret the films and report their findings.

"The new equipment will be used principally in connection with annual physical examinations," Dr. Gehrmann stated. "Chest x-rays have been a standard part of periodic examinations for twenty years, as have eye and hearing tests, blood counts, and blood and urine analyses. We also do cancer tests for women, thirty-five or over, and electro-cardiographs for men and women over forty, or when symptoms indicate the need for these examinations." Dr. Gehrmann pointed out that all of these examinations, including the x-ray, are made only with the consent of the employees.

Prior to the development of this camera, Dr. Gehrmann said, doctors were handicapped in attempting to take such a series of x-ray pictures of an individual by the danger of exposing the patient to too much radiation. The new machine surmounts this problem by decreasing the amount of radiation required to well within tolerance limits.

The heart of the machine is a photoelectric cell timing device which measures the intensity of fluorescence produced by the x-rays and automatically adjusts the exposure time of the film. The "thickness" of the patient determines the length of exposure.

PANRAY OFFERS "PANRONE"—NEW TUBERCULOSTATIC DRUG

"Panrone"—a synthetic thiosemicarbazone derivative that inhibits *M. Tuberculosis* in vitro and in vivo—is now made available to qualified investigators by the Panray Corp., manufacturers of fine medicinal chemicals.

Panrone is Panray's brand of 4-acetylaminobenzaldehyde thiosemicarbazone, whose tuberculostatic properties were first investigated in Germany by Drs. Mietzsh, Benisch, Schmidt and Domagk, and described in detail in the January 1950 issue of the American Review of Tuberculosis. Preliminary reports indicate that Panrone has antituberculous activity of the same general order as para aminosalicylic acid, and a potential toxicity somewhat like the arsenicals used in the treatment of syphillis.

The drug is available in 25 and 50 mg. tablets for investigational use. Literature may be obtained by writing to the Panray Corporation, 340 Canal Street, New York 13, New York.

Book Reviews

DIFFERENTIALDIAGNOSE DER LUNGEN RONTGENBILDER, Zeerlender. Copyright Hans Huber, Berne, Switzerland.

It is commonplace to find that a chest x-ray has been classified as tuberculosis merely on the basis of a pathological shadow. This is especially true among general practitioners, and every tuberculosis sanatorium can show a certain percentage of patients who were admitted with a diagnosis of tuberculosis because of an x-ray shadow and finally discharged with some other diagnosis after a complete work-up. Although this error is most common among men who are not chest specialists, it is a trap into which we all fall occasionally.

Zeerlender's book, "Differentialdiagnose der Lunger Rontgenbilder," Berne, 1949, is an excellent review of diseases which can be mistaken for tuberculosis. The films, as well as the postmortem findings, were selected from cases in several tuberculosis sanatoria in Switzerland. Zeerlender classified the x-ray findings into (1) parenchymal shadows, (2) paramediastinal, (3) hilar, (4) true cavities, (5) round shadows mistaken for cavities.

The first section consists of a group of films with "snow storm" type of fine nodular infiltration. Such a picture, which is ordinarily considered diagnostic for miliary tuberculosis, must be differentiated from such nontuberculous conditions as miliary bronchopneumonia, septic pneumonia, bronchiolitis, psittacosis, pneumonoconiosis, amyloidosis, and the miliary infiltration of lymphatic and myeloid leukemia, to name a few.

Medium nodular infiltration may result from sarcoid, psittacosis, undulant fever, Weil's disease, fat emboli, atelectasis, and metastasis as from osteosarcoma.

Multiple round densities (from 2 to 10 cc. in diameter, round, oval or irregular in shape, sharply circumscribed and homogeneous) may not only be tuberculous but may be also caused by lung abscesses, metastases, and cysts (including multiple exostosis of the ribs, multiple infarcts, multiple echinococci, etc.).

Single round shadows (having the same structure as the multiple ones) must be differentiated from tumors of the breast, gummas, actinomycosis, blastomycosis, aneurysm, hematomas, teratomas, chondromas, dermoid cysts, etc.

Paramediastinal shadows may be caused by spondylitis, vertebral pathology, sternal tumors or thymus hyperplasis (the latter especially in children).

Ten per cent of the cases mistaken for tuberculosis were in the group of radiating hilar lesions which must be differentiated from paribronchial sclerosis, asthma, carcinoma, polycethemia vera, etc.

Round pseudocavities may be caused by adenomas of the breast, encapsulated pneumothorax, interlobar pneumothorax or empyema, cysts, hematoma, etc.

Among the patients admitted with an erroneous diagnosis of tuberculosis, there were approximately equal numbers in the various groups: "snow storm," hilar lesions, circular shadows, and flat homogeneous shadows. The author is opposed to the practice of making a definite diagnosis from the routine postero-anterior films. A correct diagnosis

depends upon close cooperation between the clinician, the radiologist and the clinical laboratory and may entail such supplementary diagnostic measures as tomography, stereoroentgenography, thoracoscopy, bronchoscopy, diagnostic pneumothorax and biopsy.

The x-ray reproductions in this book are of excellent quality, the typography is good, and it is in general a book which can be perused with benefit by both the general practitioner and the chest specialist.

O. Neufeld, M.D.

BLAKISTON'S NEW GOULD MEDICAL DICTIONARY: First Edition. Editors, Harold Wellington Jones, M.D., Normand L. Hoerr, M.D. and Arthur Osol, Ph.D. With the cooperation of an editorial board and 80 contributors. 252 illustrations on 45 plates, 129 in color. $8.50. The Blakiston Company, Philadelphia, Toronto, 1949.

No book in the physician's library is more valuable or in greater use than the medical dictionary. Those working in medicine and closely allied fields will welcome Blakiston's New Gould Medical Dictionary. This is not a revision or another edition of an old book, but an entirely new one. This volume of 1294 pages was edited by three experts assisted by an editorial board of six persons and 80 contributors. Dr. Morris Fishbein, Editor of the *Journal of the American Medical Association*, served as editorial consultant.

Advances in medicine and closely allied fields have been so rapid and numerous over the past decade or so that many new words have appeared in the literature. This new dictionary contains all of them, together with their pronunciations and meanings. The present need for an up-to-date dictionary is greater than that of any other period during the past century except the last two decades of the 19th and the first decade of the 20th century when so much progress was made in determining etiology of various diseases as well as their treatment and prevention. The past 15 years have constituted one of the most progressive eras in the entire history of medicine with particular reference to accuracy of diagnosis, surgical techniques, chemotherapy and prevention. The users of this dictionary should not overlook the tremendous volume of work which made it possible; for example, the critical and systematic examination of over 300 standard modern texts reflecting current usage and nomenclature in all the basic fields of medicine, surgery, and the biological sciences, as well as a large number of journals, yearbooks and indices of specialties.

The indices of tables and lists and illustrative plates, the abbreviations used in definitions, explanatory notes, notes on pronunciation found in the front of the book are helpful. All defined words are in bold blackface, legible type. Pronunciation is shown by syllable division and accent, and whenever necessary by phonetic respelling.

Two hundred and fifty-two illustrations, 129 in color, are bound into the center of the book. The volume contains an appendix of 137 pages, 80 of which are devoted to anatomical tables of arteries, veins, nerves, bones, joints and muscles. The remainder of the appendix contains excellent material on diets, hormones, medical signs and symbols, organisms pathogenic to man, prescription writing, veterinary doses, vitamins, weights and measures. This dictionary should be made available to every medical student and physician as well as all working in closely allied fields.

DIE CHEMOTHERAPEUTISCHE TAMPONADE DER LUNGENKAVERNEN, Maurer, G. Georg Thieme Verlag, Stutgart, 1950.

This monograph presents a genuinely new approach to the treatment of tuberculous cavities of the lung, namely, by chemotherapeutic packing. This volume of 114 pages is of great merit, for it represents a significant departure from the much beaten path of tuberculosis therapy.

It is justly pointed out by the author that tuberculous cavities exert an overbearing influence upon the course of pulmonary tuberculosis. It is emphasized that intramuscularly given antibiotics and orally administered chemotherapeutic agents are *a priori* impotent as far as tuberculous cavities are concerned, for the structure of cavity walls obviates the access of these drugs to the inner surface of the cavity.

The new method devised by Maurer is described in a concise, easily understandable, superior didactic language. Numerous excellent technical illustrations elucidate the text and pertinent case reports offer convincing proof of the validity of the claims proferred.

Maurer's procedure comprises three basic features: (1) Speleostomy, that is, opening the cavity through the chest wall with the application of Laminaria. (2) Packing the cavity with gauze saturated with streptomycin or para-aminosalicylic acid. (3) Closure of the draining bronchus of the cavity with high-frequency current.

Speleostomy is a bloodless opening of a tuberculous cavity. It is superior to Monaldi's cavity drainage in that—among other advantages—it avoids infection of the drainage canal and also, it prevents suppuration of the chest wall at the site of intervention. In addition to the application of antibiotics and chemical compounds directly to the inner aspect of the cavity wall, Maurer's procedure permits the inspection (speleoscopy of the interior of the cavity before and during therapeutic applications. One is enabled in this manner closely to follow the process of healing and watch the gradual disappearance of tuberculous changes and their replacement by a clean, hyperemic, healing tissue.

Compared with other measures, speleostomy is not conducive to subsequent functional impairment of the lung treated, neither will it cause mediastinal shift. As an adjunct measure, the author recommends the simultaneous intramuscular injections of streptomycin or the oral administration of PAS. In well selected cases it was possible to render the tuberculous cavity sterile in the remarkably brief period of 17 days. From this it appears that speleostomy offers a cure of the tuberculous lung with a hitherto unprecedented rapidity. Needless to say it is bound to lessen the indications for thoracoplasty. Speleostomy can be used as an independent method for the treatment of moderate-sized and large cavities. Giant cavities are treated with the combination of speleostomy and thoracoplasty.

This outstanding monograph is highly recommended for the perusal of all interested in the efficient management of cavitary forms of pulmonary tuberculosis.

Andrew L. Banyai, M.D.

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Chief Resident Physician and Assistant Medical Director for J.C.R.S. Sanatorium, Spivak, Colorado. Salary commensurate with experience, plus full maintenance. Apply to Medical Director.

Applications will be received for positions of Resident and Assistant Resident at Grace Dart Home Hospital, 6085 Sherbrooke East, Montreal, Canada. Duties to commence July 1, 1951. Salary $3,000 and $2,400 respectively, with full maintenance. All aspects of medical and surgical treatment of tuberculosis. One hundred forty-five bed hospital approved by the American College of Surgeons. Apply to Medical Director.

Full time house physician, Luthern Sanatorium, Wheat Ridge, Colorado. Unfurnished house available. Salary commensurate with training. Apply to Medical Director.

Medical Director and Superintendent, Mahoning County Tuberculosis Sanatorium, 180 beds. Salary $10,000 per year plus full maintenance. Address all inquiries to Miss Kathryn L. Klee, Chairman of the Board of Trustees, Mahoning County Tuberculosis Sanatorium, City Hall, Youngstown, Ohio.

One physician wanted for residency in tuberculosis sanatorium. One fourth of all admissions nontuberculous. Surgery done by diplomate of American Board of Thoracic Surgeons. Active Out-patient service. Contact Superintendent, Hopemont Sanatorium, Hopemont, West Virginia.

POSITIONS WANTED

Associate or partnership in chest work. Experienced chest specialist. Willing to make investment. Now holding responsible position. American and graduate of Class A medical school. Excellent references. Please address all inquiries to Box 245B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Diplomate of the American Board of Surgery and Fellow of the American College of Surgeons seeks permanent position as thoracic surgeon in a sanatorium. Will locate anywhere, preferably west coast. Address all inquiries to Dr. Thomas F. Keyes, 166 Dove Street, Rochester, New York.

British physician, married, 37 years old, seeks position in a sanatorium or chest department of hospital. Excellent references from Brompton Hospital, Paddington Chest Clinic and St. Charles Hospital. Needs definite assurance of position before visa will be issued. Address all inquiries to Box 246B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

BINDING FOR COMPLETED VOLUMES

We are pleased to announce that The Book Shop Bindery, 308 West Randolph Street, Chicago, Illinois, will produce a well-bound volume at as low a price as possible for those members and subscribers who wish to preserve their issues of DISEASES OF THE CHEST. They will bind the six issues of Volume XVII in the best grade of washable buckram with gold stamping on the spine and the member's or subscriber's name in gold on the front cover. Please send the six issues to Chicago by express or parcel post prepaid with check or money order for $2.75 made payable to The Book Shop Bindery. The bound volumes will be returned with transportation prepaid by the bindery.

NOTICE TO SUBSCRIBERS

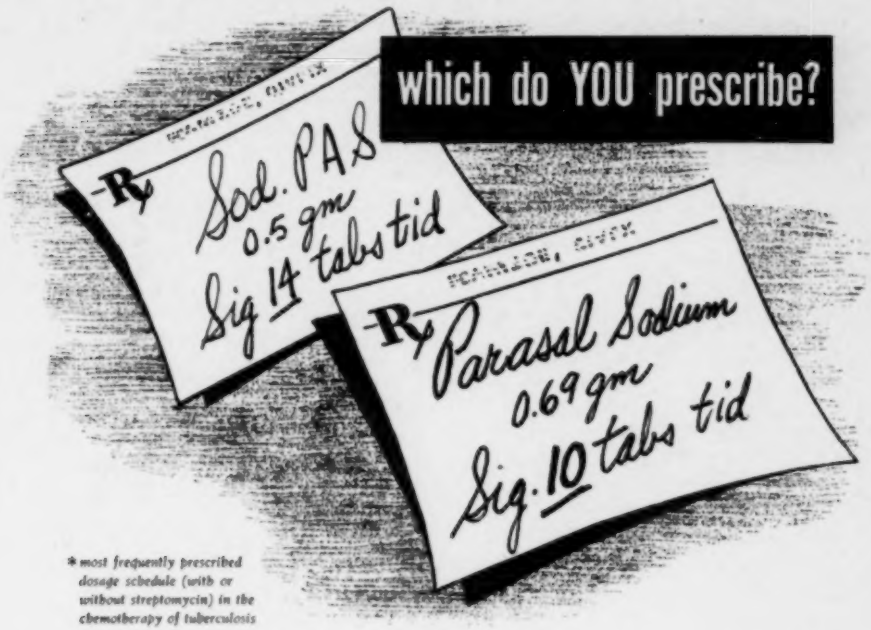
DISEASES OF THE CHEST IS NOW PUBLISHED MONTHLY

NEW SUBSCRIPTION RATES FOR TWELVE (12) ISSUES

United States of America	**$8.50 per year**
All other countries	**$9.50 per year**
Back issues	**$1.00 per copy**
Special issues (December, 1949)	**$2.00 per copy**

Jay Arthur Myers, M.D., F.C.C.P., Chairman, Editorial Board.

When 15 grams of oral PAS are indicated daily...*



* *most frequently prescribed dosage schedule (with or without streptomycin) in the chemotherapy of tuberculosis*

PARASAL SODIUM TABLETS (0.69 gm.) containing highly purified (parenteral grade) Sodium PAS, afford *fewer tablets per dose*—produce a minimum of gastro-intestinal disturbances!

Each tablet, *equivalent to exactly 0.5 gm. free PAS*, provides a neutral preparation, specially coated (non-enteric) to aid in uniform dissolution and rapid absorption.

Write today for samples and literature. Please specify product #725.

THE Panray CORP. • 340 CANAL STREET, NEW YORK 13, N. Y.

CUSTOM MANUFACTURERS OF FINE MEDICINAL CHEMICALS